

# Clinicopathological and Molecular Features of Primary Inflammatory Myofibroblastic Tumor in Nasal Cavity and Paranasal Sinuses

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**Background:** Inflammatory myofibroblastic tumor (IMT) in the nasal cavity and sinuses is rare and has special clinical and pathological characteristics with poor prognosis. This study aimed to investigate the clinicopathological and molecular features of primary IMT in the nasal cavity and paranasal sinuses.

**Methods:** The clinical features, histopathological findings, immunohistochemical findings and results of molecular genetic examination were retrospectively analyzed in 25 patients who were diagnosed with IMT in the nasal cavity and paranasal sinuses.

**Results:** Tumor tissues were mainly composed of obese spindle-shaped myofibroblasts, fibroblasts, and chronic inflammatory cells. The inflammatory cells included plasma cells, lymphocytes, eosinophils, foam histiocytes and multinuclear giant cells. Immunohistochemical staining showed the tumor was positive to anaplastic lymphoma kinase (ALK) in two patients. *ALK* fusion mutation was detected by PCR in only 1 patient.

**Conclusion:** Nasal and paranasal sinus IMTs are rare, exhibit histopathological diversity with low specificity, and require careful differentiation from inflammatory and autoimmune disorders. These tumors demonstrate a worse prognosis compared to IMTs in other anatomic locations, along with a significantly lower rate of *ALK* gene rearrangement. Identifying molecular target alterations can enhance precision diagnosis and targeted therapeutic strategies.

**Keywords:** inflammatory myofibroblastic tumor, nasal cavity, paranasal sinuses, anaplastic lymphoma kinase, clinicopathology

## Introduction

Inflammatory myofibroblastic tumor (IMT) is a unique and rarely metastatic tumor and it is mainly composed of myofibroblasts and fibroblasts, which are accompanied by the infiltration of inflammatory cells such as plasma cells, lymphocytes, and/or eosinophils.<sup>1</sup> IMT is frequently diagnosed in children and young adults. IMT can be found in multiple parts of the body, including the lungs, mediastinum, mesentery, abdomen, and pelvis. IMT in the nasal cavity and sinuses is rare and has special clinical and pathological characteristics with poor prognosis.

IMT is associated with specific gene rearrangements and aberrant signaling pathway activation. Approximately 50–60% of cases harbor *ALK* gene rearrangements, leading to *ALK* protein overexpression and activation of downstream pro-proliferative and anti-apoptotic pathways (eg, PI3K/AKT/mTOR and RAS/MAPK).<sup>2</sup> Additionally, gene fusions involving *ROS1*, *RET*, and other tyrosine kinases have been reported, suggesting that dysregulation of tyrosine kinase pathways may serve as critical driving mechanisms.<sup>3</sup> Notably, patients with nasal and paranasal sinus IMT exhibit a lower frequency of *ALK* rearrangements. Furthermore, the tumor microenvironment is characterized by abundant lymphocyte and plasma cell infiltration, implying that chronic inflammation may promote myofibroblast proliferation and tumorigenesis through cytokines such as IL-6 and TNF- $\alpha$ .<sup>4</sup> Persistent inflammatory stimuli have been proposed to induce cellular transformation via the NF- $\kappa$ B pathway.<sup>5</sup> Moreover, epigenetic regulatory abnormalities (eg, DNA methylation or

histone modification) may contribute to tumor progression by silencing tumor suppressor genes or activating oncogenes.<sup>6,7</sup>

This study retrospectively summarized the clinical characteristics, histomorphological, immunohistochemical and molecular pathological features of IMT in the nasal cavity and paranasal sinuses in 25 patients, aiming to improve the understanding of this tumor and lay the foundation for improving the precision diagnosis and treatment of IMT in the nasal cavity and paranasal sinuses.

## Materials and Methods

### Subjects

A total of 25 cases of nasal and paranasal sinus IMT with complete clinical pathological data and follow-up information were retrospectively selected from the Pathology Department of Beijing Tongren Hospital, Capital Medical University, between January 1, 2007, and December 31, 2021. All patients were newly diagnosed and untreated at the time of enrollment. The diagnosis was confirmed based on morphological and immunohistochemical findings, according to the 2022 WHO Classification of Head and Neck Tumors (5th edition).<sup>8</sup> This study was carried out following the guidelines of the Helsinki Declaration (World Medical Association Declaration of Helsinki) and was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (TREC2023-KY093). Written informed consent was obtained from each patient.

### HE Staining and Immunohistochemical Staining

1) All specimens were fixed in 3.7% neutral formaldehyde, embedded in paraffin, and then cut into sections (4  $\mu$ m) for HE staining. (2) Immunohistochemical staining: sections were processed for immunohistochemical staining using En Vision method. The primary antibodies included CK, Vimentin, SMA, MSA, Desmin, Ki-67 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd), and ALK (D5F3; Abcam Company). The presence of brownish yellow particles was regarded as positive staining. Immunohistochemistry was performed using a fully automated immunohistochemistry analyzer (Ventana BenchMark XT autostainer, Roche Ventana), and staining with diaminobenzidine (DAB) served as a control.

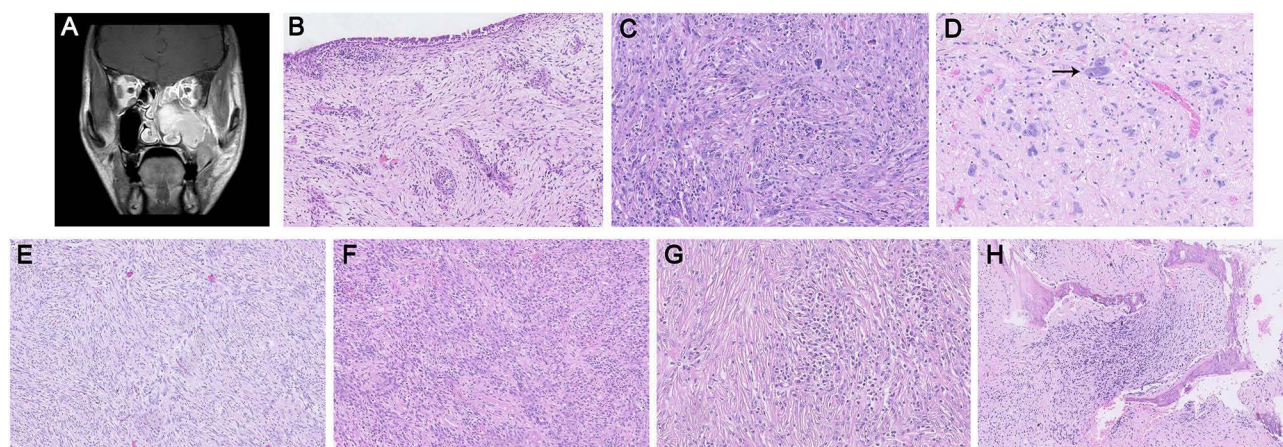
### Molecular Examination

1) detection of ALK gene rearrangement by FISH: the ALK gene breakage recombination detection kit (Abbott, United States) was used for the detection of ALK gene rearrangement according to manufacturer's instructions. The red signals and green signals can be seen separately under the microscope in the presence of ALK gene breaks, which suggests the ALK gene breaks and fusion. Criteria for interpretation: At least 50 tumor cells were observed, and ALK FISH positive could be confirmed if the separation of red signals and green signals was observed in more than 25 cells (>50%); if the separation of red signals and green signals was observed in 5–25 cells (10–50%), additional 50 cells should be examined; among 100 cells examined, ALK FISH positive could be confirmed if the separation of red signals and green signals was observed in more than 15 cells (15%). The known lung cancer cells served as a positive control. (2) PCR Detection: The detection was performed using the human ALK gene fusion detection kit (Lot No.: 8.01.263.1W006A) manufactured by Amoydx Biotech Co., Ltd. (Xiamen, China) Due to commercial confidentiality requirements, the specific primer sequences of this kit are not publicly disclosed. The experimental procedures were strictly implemented in accordance with the manufacturer's instructions.

## Results

### Clinical Features

Among 25 patients with IMT in the nasal cavity and sinuses, there were 15 males and 10 females. The age at onset ranged from 13 months to 69 years, the average age was 34 years and the median age was 31 years. The most common sites were maxillary sinus and nasal cavity (Figure 1A), and the tumor often involved the orbit, followed by the pterygopalatine fossa and ethmoid sinus. Additionally, it also affected the sphenoid sinus, skull base, infratemporal fossa, and parotid gland. The clinical symptoms varied depending on the location and extent of the tumor. The most



**Figure 1** (A) A mass in the left maxillary sinus was found on enhanced MRI (T1WI). There was obvious uniform enhancement and expansive growth for the mass with partial protrusion into the nasal cavity. (B) Spindle shaped cell proliferation was found in the ciliated columnar epithelial mucosa of interstitium, which was accompanied by a large number of plasma cells and lymphocytes infiltrated. HE staining (low magnification). (C) Evidence cellular atypia was observed in 1 patient with nuclear division in some cells (HE staining; high magnification). (D) The tumor cells appeared as obese spindle shaped, with eosinophilic cytoplasm (red) and obvious nucleoli. Ganglion-like cells were observed. (HE staining; high magnification). The arrow points to tumor cells with obvious partial atypia, which are similar to ganglion-like cells. (E) Hyperplasia of myofibroblasts and bundle-like interwoven fibroblasts with loose, edematous and mucinous stroma in the tumor (HE staining; moderate magnification). (F) The tumor cells were spindle shaped and arranged in a woven pattern, with infiltration of inflammatory cells. Collagen bundles were in some areas (moderate magnification). (G) A large amount of plasma cell infiltrated in some areas, (HE staining; moderate magnification). (H) The tumor invaded bone tissues (HE staining; moderate magnification).

common symptoms were nasal congestion, runny nose, and headache. Other local symptoms included difficulty opening the mouth, toothache, decreased vision, diplopia, and eyeball protrusion. The follow-up information was complete in 17 patients (Table 1) and the duration of follow-up ranged from 10 months to 136 months (median: 57 months). Among them, recurrence was not observed in 10 patients; 2 patients with recurrence still survived and 5 patients died (4 died due to multiple systemic metastases and 1 died of cerebrovascular disease).

## Pathological Features

Upon macroscopy, the tumor was hoar or taupe, had a delicate texture and appeared as a vortex or mucus like mass. In a few cases, hemorrhage and necrosis were visible. On microscopy, the tumor was composed of spindle-shaped myofibroblasts, fibroblasts, and chronic inflammatory cells. The spindle-shaped cells were arranged in bundles or mats, with pale eosinophilic cytoplasm (Figure 1B), oval-shaped nuclei, fine chromatin, and small red nucleoli. Necrosis was noted in 1 patient; evident cellular atypia with nuclear division was found in 1 patient (Figure 1C). Big myofibroblasts with vesicular nuclei and prominent nucleoli similar to those of ganglion cells were observed in 2 cases (Figure 1D). Inflammatory cells included plasma cells, lymphocytes, eosinophils, foam like tissue cells and multi-nucleated giant cells. Edema and mucinous changes were observed in the tumor stroma (Figure 1E), and collagen bundles (Figure 1F) and extensive plasma cell infiltration were noted in several areas (Figure 1G). Tumor invasion into bone tissues was observed in 4 cases (Figure 1H).

## Immunohistochemical Staining

Immunohistochemical staining was performed in 25 patients. All the tumors were negative to CK but positive to Vimentin; 18 tumors were positive to SMA (18/25) (Figure 2A), 10 positive to MSA (10/25), and 6 positive to Desmin (6/25); the Ki-67 index ranged from 2% to 40%; in 2 cases, the nucleoplasm was strong positive to ALK (Figure 2B).

## Molecular Examination

ALK gene rearrangement was not found in all patients on FISH (Figure 2C). ALK fusion gene PCR was performed in all patients. Results showed that in 2 patients who were negative to ALK immunohistochemistry but positive to ALK FISH, 1 patient had ALK fusion mutation on PCR (Figure 2D) and the other patient had no mutation. Mutation was not found in

**Table 1** Clinical and Pathological Characteristics of 25 Patients with IMT in the Nasal Cavity and Sinuses

No	Gender	Age (yr)	Clinical Manifestations	Imaging Examination	ALK (D5F3)	FISH	RT-PCR	Treatment	Duration of Follow Up (Months)
1	Male	19	Nasal congestion, nasal bleeding, and periodontal radiation pain	Left nasal cavity and maxillary sinus	Negative	Negative	Negative	Radical surgery	22, No recurrence, no metastasis
2	Female	31	Right runny nose and intermittent pain in the right temporal region	Right maxillary sinus and infratemporal fossa	Negative	Negative	Negative	Radical surgery + radiotherapy	136, No recurrence, no metastasis
3	Female	37	Right facial pain, right zygomatic arch swelling pain	Right maxillary sinus	Negative	Negative	Negative	Radical surgery +radiotherapy + steroid therapy	Lost to follow up
4	Female	56	Numbness around the left nasal wing, tear overflow in the left eye, diplopia	Right maxillary sinus	Negative	Negative	Negative	Radical surgery +steroid therapy	119, No recurrence, no metastasis
5	Male	62	Left facial numbness	Left maxillary sinus and orbit	Negative	Negative	Negative	Radical surgery +radiotherapy +chemotherapy +steroid therapy	54, Died
6	Male	31	Cranioorbital mass	Left eye orbit and pterygopalatine fossa	Negative	Negative	Negative	Tumor resection +steroid therapy	Lost to follow up
7	Male	69	Puss discharge from the nose and nasal congestion	Right maxillary sinus	Negative	Negative	Negative	Radical surgery + radiotherapy	47, No recurrence, no metastasis
8	Male	25	Nasal congestion, discomfort in the right eye, and increased secretion	Right frontal sinus and orbit	Positive	Negative	Negative	Tumor resection	74, No recurrence, no metastasis
9	Female	24	Tumor at the inner canthus of the right eye	Bilateral ethmoid sinus, sphenoid sinus, maxillary sinus, nasal cavity, and orbit	Negative	Negative	Negative	Radical surgery +radiotherapy +chemotherapy	30, Recurrence
10	Female	54	Pain and swelling in the right face, protrusion of the eyeball, low-grade fever, and decreased vision	Right nasal cavity, orbital cavity, ethmoid sinus, and pterygopalatine fossa	Negative	Negative	Negative	Only tumor biopsy due to wide invasion	Lost to follow up

(Continued)

Table 1 (Continued).

No	Gender	Age (yr)	Clinical Manifestations	Imaging Examination	ALK (D5F3)	FISH	RT-PCR	Treatment	Duration of Follow Up (Months)
11	Female	67	Right nasal congestion and nosebleeds	Right maxillary sinus and nasal cavity	Negative	Negative	Negative	Radical surgery (history of cerebral infarction)	19, Died
12	Female	9	Mass at left lower eyelid	Right maxillary sinus, lacrimal sac, and lower eyelid	Negative	Negative	Negative	Radical surgery +radiotherapy +steroid therapy	Lost to follow up
13	Male	41	Right facial numbness and diplopia	Right maxillary sinus and orbit	Negative	Negative	Negative	Radical surgery +radiotherapy +steroid therapy	93, No recurrence, no metastasis
14	Male	29	Left nasal dorsal mass and tear overflow	Left lacrimal sac area, nasal dorsum, and eyelids	Negative	Negative	Negative	Tumor resection +radiotherapy +chemotherapy	45, No recurrence, no metastasis
15	Male	14 months	Right nasal mass, tear overflow, nasal congestion, and intermittent fever	Right inner canthus, maxillary sinus, and nasolacrimal duct	Positive	Negative	Positive	Tumor resection +chemotherapy	Lost to follow up
16	Female	64	Right nose bleeding and decreased left eye vision	Right sphenoid sinus and maxillary sinus	Negative	Negative	Negative	Tumor resection +radiotherapy +chemotherapy +steroid therapy	10, Recurrence
17	Male	30	Right nasal congestion and decreased sense of smell	Nasal septum and right nasal cavity	Negative	Negative	Negative	Tumor resection+steroid therapy	14, No recurrence, no metastasis
18	Male	20	Numbness and pain in the left facial area	Left maxillary sinus	Negative	Negative	Negative	Tumor resection +radiotherapy +steroid therapy	21, died
19	Female	31	Right eyeball protrusion, headache, nosebleeds, and decreased vision	Right maxillary sinus	Negative	Negative	Negative	Tumor resection +radiotherapy	Lost to follow up

(Continued)



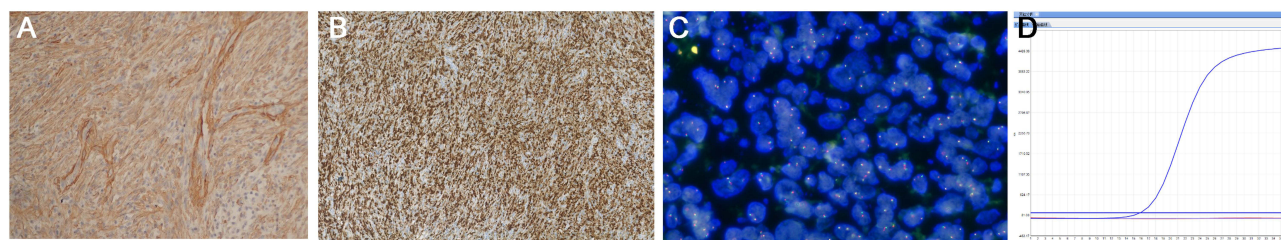
**Table 1** (Continued).

No	Gender	Age (yr)	Clinical Manifestations	Imaging Examination	ALK (D5F3)	FISH	RT-PCR	Treatment	Duration of Follow Up (Months)
20	Male	30	Right bloody rhinorrhea, nasal congestion, right toothache, right face numbness, and right headache	Right maxillary sinus, right nasal vestibule	Negative	Negative	Negative	Radical surgery + radiotherapy	21, died
21	Male	13 months	Left cheek swelling, gum swelling, and fever	Left maxillary sinus, infratemporal fossa, pterygopalatine fossa, and alveolar bone	Negative	Negative	Negative	Tumor resection	92, No recurrence, no metastasis
22	Male	62	Left persistent nasal congestion, runny nose, temporal headache, and decreased sense of smell	Left maxillary sinus	Negative	Negative	Negative	Radical surgery +radiotherapy +chemotherapy	93, died
23	Female	39	Left nasal congestion, runny nose, left cheek swelling and pain, and decreased sense of smell	Left maxillary sinus	Negative	Negative	Negative	Radical surgery +radiotherapy +chemotherapy +steroid therapy	Lost to follow up
24	Male	21 months	Left eye protrusion for 15 days, persistent nasal congestion and runny nose on the left side	Left maxillary sinus	Negative	Negative	Negative	Tumor resection	Lost to follow up
25	Male	25	Nasal congestion, runny nose, and headache	Left pterygopalatine fossa	Negative	Negative	Negative	Tumor resection +steroid therapy	131, No recurrence, no metastasis

remaining 23 patients who were negative to ALK immunohistochemistry. Our cohort identified only one ALK-positive patient, a child who achieved complete surgical resection with no evidence of recurrence or metastasis during follow-up, demonstrating an excellent prognosis.

## Discussion

IMT was first identified in the lungs. IMT is often found in the lungs, abdomen, and pelvis of children and young adults, and is prone to local recurrence.<sup>1</sup> Generally, it is usually a localized single lesion, and multifocal or metastatic IMT is uncommon. Approximately 15–25% of IMT is found in the head and neck, and the vocal cords in the throat, maxillary sinus, and oral cavity are the most common sites. In the 2022 WHO Classification of Head and Neck Tumors (fifth edition), the ICD code of IMT is classified as 1,<sup>8</sup> it is classified as a tumor with low malignant potential, with high



**Figure 2** (A) Immunohistochemical staining shows SMA positivity in tumor cells (EnVision method; moderate magnification). (B) Immunohistochemical staining showed diffuse strong ALK (D5F3) positivity in the cytoplasm of tumor cells (EnVision method; moderate magnification). (C) Strong nuclear ALK positivity on immunohistochemistry in 2 cases, but FISH failed to identify gene rearrangement. (D) ALK positivity on immunohistochemistry in 1 case, but FISH showed negative to ALK. Further PCR revealed ALK fusion mutation.

recurrence and low metastasis risk after resection. Available studies have shown that IMT in the nasal cavity and sinuses is more invasive as compared to IMT in other sites,<sup>9</sup> but it is uncertain whether this is due to the invasive characteristic of IMT or incomplete resection because of complex anatomical location of the head and neck. In the present study, among 17 patients who received follow up, 2 patients developed recurrence and 4 died of related diseases (6/17; 35.3%). Zhang et al investigated 10 patients with IMT in the bladder and 6 patients in the uterus, and results showed no recurrence or metastasis during follow up period, and the prognosis of IMT in the head and neck was significantly worse than in that in other sites.<sup>10,11</sup> Therefore, sufficient attention should be paid to the clinical diagnosis and treatment of IMT in the head and neck. The WHO Classification of Head and Neck Tumors (fifth edition) describes that the larynx is the most common site of IMT in the head and neck.<sup>8</sup> In the present study, only 3 patients with IMT in the head and neck were diagnosed with IMT in the larynx, which was significantly lower than the incidence of IMT in the nasal cavity and sinuses. On imaging, the tumor shows diffuse invasive growth in the nasal cavity and sinuses, and it often invades surrounding tissues. The most common sites affected by the IMT are the maxillary sinus, nasal cavity, and orbit, followed by the pterygopalatine fossa and ethmoid sinus. In addition, sphenoid sinus, skull base, infratemporal fossa, and parotid gland may also be involved by the IMT. In our cases, the most common symptoms were nasal congestion, runny nose, and headache; other local symptoms included difficulty in opening the mouth, toothache, decreased vision, diplopia, and eyeball protrusion. On the microscopy, myofibroblasts and fibroblast proliferation were observed with infiltration of plasma cells, lymphocytes, eosinophils, and histiocytes. The lesions included fibrous histiocytoma like subtype and nodular fasciitis subtype. Tumor cells were spindle shaped with round nuclei containing 1–3 nucleoli. The presence of mucinous cell stroma, ganglion like cells, giant cells, necrosis and lymphatic vessel infiltration, high mitotic activity, increased cell number, and boundary infiltration are considered as factors of poor prognosis.<sup>1</sup> The immunohistochemical staining aims to identify myofibroblasts in the IMT and exclude other diagnoses. In most cases, the spindle-like cells are positive to Vimentin, SMA, and MSA. Vimentin positive reaction is usually strong, and Vimentin expression is diffuse in the cytoplasm of spindle-like cells, but occasionally focal positive cells are observed. The SMA and MSA positivity may be diffuse or focal, while the tumor is negative to Desmin or focally positive to Desmin, which are consistent with the characteristics of myofibroblasts with differentiation. These findings were also consistent with the results observed in this study. Koirala et al found that focal CK positivity was observed in about one-third of IMT with occasional diffuse CK expression.<sup>12</sup> Ke et al reported two cases of IMT in the urachus and bladder and the tumor cells showed strong positive to ALK, CK, and LCK in the cytoplasm on immunohistochemistry, while the tumor cells were negative to HCK and myogenic markers.<sup>13</sup> This is very rare and has not been reported in previous urinary IMT. In the present study, the IMT in the nasal cavity and paranasal sinuses was negative to CK, but partially expressed myogenic markers.

Clinical studies have shown that approximately 50–60% of IMTs express anaplastic lymphoma kinase (ALK). ALK gene encodes a single-chain transmembrane highly conserved receptor tyrosine kinase (RTK) composed of 1620 amino acids. ALK protein consists of three domains, including extracellular ligand binding domain (1030aa), transmembrane domain (28aa), and intracellular tyrosine kinase domain (561aa). Under physiological conditions, extracellular ligands can induce the coupling between two transmembrane ALK proteins, thereby activating intracellular signaling pathways to exert biological effects. ALK is highly expressed in the brain and nervous system during embryonic development and its expression rapidly decreases after birth.<sup>14</sup> Most IMT with ALK rearrangement is often confirmed by the presence of

cytoplasmic or nuclear positivity on immunohistochemistry, which also helps differentiate them from other similar tumors. Lahlou et al found that the incidence of ALK rearrangement in the IMT of nasal cavity and sinuses was lower than that in other sites.<sup>15</sup> Zhu et al reported 13 cases of IMT in the nasal cavity and sinuses, and ALK rearrangement was observed in only 1 patient.<sup>9</sup> In the present study, ALK rearrangement was found in only one patient aged 14 months, which was consistent with high prevalence of ALK rearrangement in children and young adults. In addition, some studies investigate the sensitivity and specificity of ALK1, ALK (5A4), and ALK (D5F3) clone antibodies in detecting ALK rearrangement, and results showed that ALK (D5F3) was the most effective biomarker for ALK gene rearrangement.<sup>10</sup> In our study, 2 patients positive to ALK (D5F3) on immunohistochemistry received further FISH and results showed negative. However, one patient was positive to ALK on PCR (the other was negative). In remaining 23 patients negative to ALK (D5F3) on immunohistochemistry, both FISH and PCR still showed negative to ALK (D5F3). This indicates that immunohistochemistry for ALK (D5F3) can be employed for the initial screening of IMT. If positive, FISH can be performed for validation. When FISH shows negative, PCR or NGS can be employed to confirm the ALK gene rearrangement. If it is negative, additional molecular examination is unnecessary, and immunohistochemistry can serve as a good alternative. FISH has high requirements for tissue processing: the tumor tissues should be embedded in paraffin within 2 years; there are time limits for tissue fixation and dehydration, and the pathologists should receive training for the operation and result interpretation of FISH. In addition, when the rearrangement is caused by complex events or rearrangement occurs in small genomic regions of chromosomes, false negative is common on FISH. This may explain the negative result on FISH in 1 patient who was positive to ALK on immunohistochemistry and PCR.

ALK gene fusion is the most common genetic abnormality in IMT of the head and neck, with TIMP3 being the most common (about 50%) fusion partner.<sup>8</sup> ALK kinase inhibitor can competitively bind to the ALK kinase region, which then blocks downstream signaling pathways of ALK and achieving therapeutic effects on the tumor.

Notably, the distribution of fusion genes varies across IMT subtypes: FN1-ALK fusion is relatively common in bladder IMT but rare in other anatomic locations.<sup>10</sup> In female genital tract IMTs, ALK rearrangement positivity can exceed 80%, typically involving TPM3 or TPM4 fusion partners, with less frequent occurrences of CLTC, CARS, ATIC, and BRNBP2 fusions.<sup>11</sup>

The ALK fusion mutation, termed the “diamond mutation” in lung cancer due to its exceptional therapeutic response, has revolutionized treatment strategies. Third-generation ALK inhibitors (eg, lorlatinib) achieve a 5-year progression-free survival (PFS) rate of 60% in advanced ALK-positive NSCLC patients and reduce the risk of brain metastatic progression by 94%.<sup>16</sup> As a primary driver mutation in anaplastic large cell lymphoma (ALCL), ALK rearrangement occurs in approximately 60% of pediatric cases. FDA-approved ALK inhibitors like crizotinib have demonstrated an objective response rate exceeding 80% in relapsed/refractory ALCL, significantly extending overall survival.<sup>17</sup>

In addition, there are other types of tyrosine kinase fusion and complex genetic abnormalities in IMT. In a study on IMT in the duodenum of a 37-year-old male, immunohistochemistry, FISH, RNA detection, and PCR showed negative results, but NGS revealed fusion of FN1 and IGF1R.<sup>18</sup> In addition, a study has reported two cases of NTRK-ETV 6 fusion positive IMT in which both nucleus and cytoplasm were positive to pan-TRK, but some non-IMT tumor cells which were positive to NTRK-ETV 6 were positive to pan-TRK in the cytoplasm. This indicates that pan-TRK positive nucleus and cytoplasm may help to identify ETV 6-NTRK 3 positive IMT and is also helpful for the identification of patients which can benefit from Trk-targeted therapy.<sup>19</sup> Conventional pathological examinations have limitations in the detection of these complex gene mutations, and NGS provides an effective tool for the accurate identification of gene fusion, which contributes to the differential diagnosis of IMT and is also helpful for the targeted therapy in IMT patients.<sup>20</sup> Therefore, for the patients with initial diagnosis of IMT, NGS is recommended if targeted therapy will be employed. This pilot study has inherent limitations including small sample size, retrospective design, and restricted molecular testing capacity. Future investigations aim to address these gaps through prospective collection of fresh specimens for comprehensive whole-exome sequencing, transcriptomic analysis, and cell line studies to identify IMT-specific molecular signatures. The application of next-generation sequencing (NGS) will expand our understanding of IMT fusion gene subtypes while elucidating the relationship between genetic alterations and pathological features remains critical.



Inflammatory fibrous lesions in the nasal cavity and sinuses are very common in clinical practice, and IMT should be differentiated from following diseases.

1) Nasal polyps: a large number of inflammatory cells can be seen in the stroma of nasal polyps. Sometimes, there may be scattered spindle-like fibroblasts with dark nuclei in the subcutaneous areas or around vessels. These cells are generally not patchy, and nuclear division is rare. 2) IgG4-related diseases: There is infiltration of a large number of inflammatory cells and fibrosis, and the morphological features overlap with some of IMT. However, the fibrosis of IgG4-related diseases in the nasal cavity and sinuses is characteristic: concentric “onion like” fibrosis is present around the small salivary glands in the mucosa, lymphocytes and plasma cells are the dominant inflammatory cells, and especially the number of IgG4 positive plasma cells is larger than 10/HPF, which is accompanied by the increased serum IgG4 and swelling of the lacrimal gland, parotid gland or submandibular gland areas. 3) Rhinoscleroma at sclerosis stage: the general manifestation of this disease is the fragile polyp in the nasal cavity. Microscopically, there is infiltration of inflammatory cells, including lymphocytes, plasma cells, neutrophils and foam-like histiocytes. Warthin-Starry staining can identify *Klebsiella rhinoscleromatis* in cells. Fibrosis occurs as the disease progresses, but usually, there are no spindle-shaped fibroblasts. 4) Spindle-shaped squamous cell carcinoma, spindle-shaped malignant melanoma, etc: the spindle-shaped neoplastic lesions can be identified through a group of related specific immunohistochemical antibodies.

The treatment for IMT mainly includes surgery, radiotherapy, chemotherapy, and glucocorticoid therapy, either alone or in combination. In 5 patients died during follow-up period, 1 patient with a history of cerebral infarction only underwent radical surgery, and the remaining patients received comprehensive treatment. The presence of protein produced by the fusion genes such as anaplastic lymphoma kinase (ALK), tyrosine protein kinase (ROS1), and neurotrophin tyrosine kinase receptor 1 or 3 (NTRK1/3) can be used as an indication of tyrosine kinase inhibitor (TKIs) therapy. For patients with negative results in ALK immunohistochemistry, second-generation sequencing can be employed to identify the change in the specific gene, which may guide the following treatment and prognosis prediction.

In summary, IMT of the nasal cavity and sinuses is rare, and the range of age at onset is large, its histological features are diverse, and there are no specific features for this type of tumor, which increase rates of misdiagnosis and missed diagnosis. WHO classifies IMT as a tumor with low malignant potential, but the prognosis of IMT in the nasal cavity and sinuses is significantly worse than that of IMT in other sites. In addition, the incidence of ALK gene rearrangement in the IMT of the nasal cavity and sinuses is significantly lower than that of IMT in other sites. The molecular pathogenesis of IMT in the nasal cavity and sinuses is still poorly understood. Subsequent studies will focus on larger multi-center studies and multi-dimensional analyses of tumor microenvironments and oncogenic pathways to establish precision diagnostics and therapeutic targets for IMT.

## Disclosure

The authors report no conflicts of interest in this study.

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