Inflammatory myofibroblastic tumor in the head and neck—a neoplasm with both tumor features and inflammation

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Objective. The aim of this study was to unveil the reciprocal relation of tumor characteristics and inflammation in inflammatory myofibroblastic tumor in the head and neck.

Study Design. The study included a retrospective cohort of patients with inflammatory myofibroblastic tumors treated between 2005 and 2017 in a tertiary hospital. Tumor features and inflammation were assessed through the expression of anaplastic lymphoma kinase (ALK), the degree of inflammation and cyclooxygenase-2 (COX-2) expression. The prognostic factors were analyzed for overall survival (OS) and disease-free survival (DFS) in univariate and multivariate analyses.

Results. Forty-one patients diagnosed with inflammatory myofibroblastic tumors were followed up, and 41 paraffin sections were obtained. The positive rate of ALK expression was 21 (51.2%) of 41 patients. Nineteen patients had high-grade ALK expression, and 22 patients had low-grade ALK expression. Thirty-nine patients had high-grade inflammation, and 2 had low-grade inflammation. The positive rate of COX-2 expression was 100%. Tumors with both high-grade ALK expression and inflammation had worse DFS ($P = .015$). The multivariate Cox analysis showed that the grades of ALK expression and inflammation ($P = .004$) were independent risk factors for DFS.

Conclusions. Because of the latent synergistic effects of ALK and inflammation in the tumorigenesis of inflammatory myofibroblastic tumor, the combined therapy of ALK and COX-2 inhibitors shows promise. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e316−e323)

An inflammatory myofibroblastic tumor (IMT) is defined as an intermediate (rarely metastasizing) soft tissue tumor that is histopathologically characterized by a heterogeneous group of fibroblastic or myofibroblastic spindle cells with the infiltration of plasma cells, lymphocytes, and eosinophils.[1] The predominant location is the lung, followed by the abdomen and the pelvis.[2] It is difficult to diagnose and treat an inflammatory myofibroblastic tumor in the head and neck (HNIMT), which accounts for 5% of all IMTs and 14% to 18% of all extrapulmonary IMTs.[3]

Formerly, IMT was considered an abnormal reaction manifesting as proliferation of myofibroblastic cells as a result of long-term chronic stimulation of microbiologic infection, tissue damage, or allenthesis.[4] Because of the pathologic traits of an IMT, it was once called *inflammatory pseudotumor, plasma cell granuloma, inflammatory fibrosarcoma*, among other names.[5] In 1939, Brunn reported an inflammatory reaction in the lung that exhibited the biologic behavior of tumors, such as invasive growth, recurrence, and metastasis, and is now deemed an IMT.[6] It was not until 1997 that Sciot et al. found the rearrangement of the *anaplastic lymphoma kinase (ALK)* gene, thus demonstrating IMT as a type of true neoplasm instead of an inflammatory reaction.[7] Hence, IMT is believed to be a tumor with inflammatory features. ALK is a widely accepted tumor marker for IMT. It has been reported that the aberrant expression of ALK exists in approximately 50% of IMTs and has been attributed to the rearrangement of the *ALK* gene locus on 2p23.[8] According to some reports, the COX-2 inhibitor celecoxib can shrink the tumor size and control the growth rate of some IMTs with nonsurgical indications by alleviating inflammation,[9] thus making COX-2 an underlying candidate for the inflammatory features of IMTs.

So far, most reports on HNIMT have been those of case studies that focused on ALK expression alone. This study aims to review the tumor and inflammatory features of HNIMT, especially with regard to ALK and COX-2 expression, to explore their mutual relationship, to identify valuable prognostic factors, and to provide new ideas for targeted treatment.

Statement of Clinical Relevance

The inflammatory myofibroblastic tumor in the head and neck has both inflammation and tumor features and is difficult to diagnose and treat.

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MATERIALS AND METHODS

Ethics approval was granted by the Ethical Committee of the Shanghai Ninth People's Hospital affiliated with the Shanghai Jiaotong University School of Medicine. Informed consent for participating in the clinical study was signed by all involved patients. Data on all 51 histologically proven HNIMTs treated from 2005 to 2017 were retrieved from a database from the Department of Oral and Maxillofacial Head Neck Oncology in a tertiary referral hospital. All patients underwent radical resection of the primary tumor. The data acquired included demographic details, medical history, clinical features, histopathologic characteristics, and follow-up information. A total of 41 paraffin slides were available and were reviewed by experienced pathologists.

On the basis of our previous research, the tumor site was cataloged over the plane of the ala-tragus line and the one below it.[3] Tumor size was defined as the maximum dimension measured on computed tomography (CT) or magnetic resonance imaging (MRI). All the measurements were done under the guidance of professional radiologists. Receiver operating characteristic curves were generated to determine the cutoff values for tumor size.

According to the World Health Organization (WHO) soft tissue classification, all 41 specimens were divided into 3 histopathologic types: myxoid, compact, and hyalinized.[1] Briefly, the myxoid type was rich in the myxoid background with loose spindle cells (e.g., nodular fasciitis). The compact type comprised dense spindle cells arranged in fascicles and swirls with infiltration of inflammatory cells (e.g., fibrous histiocytoma). The hyalinized type was mainly composed of cellular collagen (e.g., desmoid or a scar). On the basis of the research of Bennett, the degree of inflammation was graded as mild (obvious at high power, × 200), moderate (obvious at medium power, × 100) and severe (obvious at low power, × 40). The high-grade group included specimens with moderate and severe degrees of inflammation, and the low-grade group included specimens with a mild degree and negative inflammation.[10] Tumor malignancy was distinguished according to pathology based on tumor atypia and aberrant mitoses. The mitosis count was made by using high-power magnification (high-power field [HPF]) throughout 10 successive fields chosen in the most mitotically active areas. A score of 1 was attributed to lesions that displayed 0 to 9 mitoses per 10 HPF, a score of 2 to lesions that displayed 10 to 19 mitoses per 10 HPF, and a score of 3 to lesions that showed greater than 20 mitoses per 10 HPF. In our study, HNIMTs with a mitosis score of 3 were considered malignant.[11,12]

Immunohistochemistry was performed with the following different ALK monoclonal antibody types, which were used to reduce the false-negative rate (all were obtained from Celerus Diagnostics, Brisbane, CA): ALK-1, ALK-SP8, ALK-DF53, and ALK-1A4. Anaplastic large cell lymphoma was used as the positive control. Similarly, the COX-2 monoclonal antibody (purchased from Celerus Diagnostics, Brisbane, CA) was used to examine COX-2 expression, and colon cancer was used as the positive control. The intensities of cytoplasmic staining of ALK and COX-2 expression were classified as negative (−), mild (+), medium (++), and strong (+++) based on staining intensity and dyeing range. To be more specific, the intensity of cytoplasmic staining was classified as 0 (negative) or 1+/2+/3+ (mild/medium/strong). The dyeing range was classified as 0: < 10%; 1: 11% to ~30%; 2: 31% to ~70%; 3: ≥ 71% (5 fields under high power). The degree of ALK and COX-2 expression was the product of the score of staining intensity and dyeing range, which was negative (−) for 0; mild (+) for 1 to 2; medium (++) for 3 to 4; and strong (+++) for 6 to 9. ALK and COX-2 expression was divided into 2 grades: (1) high-grade group, which included the medium- and strong-staining groups; and (2) low-grade group, which included the mild- and negative-staining groups.[13] The Ki-67 index was bifurcated into high or low, depending on the average number of Ki-67−positive cells being less than 50%.[14]

Overall survival (OS) was defined as the time interval from the date of surgery to the time of death or the last follow-up, and disease-free survival (DFS) was defined as the time interval from the date of surgery to the date of first local recurrence or the last follow-up. Statistical analysis was performed with SPSS version 16.0 software (SPSS Inc., Chicago, IL). Pearson's χ^2 test and Fisher's exact test were used. Both OS and DFS were calculated by using the Kaplan-Meier method. The significant differences of various factors were determined through a log-rank test and univariate Cox regression. The factors that showed significance were then included in the multivariate Cox proportional hazards model. *P* values were 2-sided and were considered statistically significant if less than 0.05.

RESULTS

Patient demographic characteristics

Between January 2005 and December 2017, a total of 51 successive patients with HNIMTs underwent radical surgery in our hospital. A summary of the patients' data is presented in Table I. Sixteen patients (39%) were males, and 25 (61%) were females. The gender ratio was 1:1.56. The median age was 36 years, and the age distribution shows 17 patients (41.5%) age 40 years or greater (range 4−73 years). The receiver operating characteristic revealed 4 cm as the optimal cutoff for tumor size, with 13 patients (31.7%) having tumors 4 cm or less in size and 28 (68.3%) having tumors greater than 4 cm in size. With regard to the location, 21 patients (51.2%) had tumors over the ala-tragus line, and 20 (48.8%) had tumors below it. All of the patients had undergone

Table I. Patient demographic characteristics

Variable	*No.(%)*
Age (years)	
≤ 40	24 (58.5%)
> 40	17 (41.5%)
Gender	
Male	16 (39%)
Female	25 (61%)
Tumor size	
≤ 4 cm	13 (31.7%)
> 4 cm	28 (68.3%)
Tumor location	
Below the ala-tragus line	21 (51.2%)
Over the ala-tragus line	20 (48.8%)
Histologic subtype	
Myxoid type	9 (22%)
Compact type	8 (19.5%)
Hyalinized type	24 (58.5%)
Grade of inflammation	
Low grade	2 (4.5%)
High grade	39 (88.6%)
Grade of ALK	
Low grade	22 (53.7%)
High grade	19 (46.3%)
Grade of ALK and inflammation	
Low grade	24 (58.5%)
High grade	17 (41.5%)
Malignancy transformation	
Yes	19 (37.3%)
No	32 (62.7%)
Ki-67 index	
High	15 (46.9%)
Low	17 (53.1%)

ALK, anaplastic lymphoma kinase.

definitive treatment with surgery, and a total of 19 patients (37.3%) received postoperative radiotherapy.

A review of the histopathologic subtypes revealed 9 myxoid-type (22%), 8 compact-type (19.5%), and 24 hyalinized-type (58.5%) tumors. Abundant vascular proliferation could be observed in tumor tissues, with some forming staghorn morphology. Hemorrhage and necrosis were very common. The spindle cells were often inserted into the striated muscles. Mucinous and hyaline degeneration was observed in most specimens (Figure 1A). Nineteen (37.3%) samples had malignancy transformation (Figure 1E).

Expression of ALK and COX-2

The total positive rate of ALK was 21 (51.2%) of 41. Seventeen specimens showed positive responses to ALK-1, of which 8 were mild, 7 were medium, and 2 were strong. Most staining was located in the cytoplasm of spindle cells. Eighteen specimens showed positive responses to ALK-SP8, of which 12 were mild, 3 were medium, and 3 were strong. Most staining was located in the cytoplasm of spindle cells. Only 4 specimens showed positive responses to ALK-D5F3, and 2 showed positive responses to ALK-1A4. Most staining of ALK-D5F3 and ALK-1A4 was located in the cytoplasm and the nuclear membrane. According to dyeing range and staining intensity, 19 patients had high-grade ALK expression, of which 14 exhibited medium expression and 5 exhibited strong expression; and 22 patients had low-grade ALK expression, of which 20 exhibited negative expression and 2 exhibited mild expression. Representative images of negative, moderate, and strong ALK immunohistochemical staining in HNSCC tissues are presented in Figure 1C.

A total of 27 patients (60%) showed a moderate degree of inflammation, followed by 12 (26.7%) with a severe degree and 6 (13.3%) with a mild degree. Thirty-nine patients had high-grade inflammation, and 6 had low-grade inflammation. The inflammatory cells were scattered among the spindle cells in most specimens, whereas some gathered to form germinal centers (Figure 1B).

The positive rate of COX-2 expression was 41 (100%) of all 41, of which 16 specimens were mild, 13 were medium, and 16 were strong (Figure 1D).

ALK was related to the Ki-67 index

As shown in Table II, ALK expression was not related to gender ($P = .330$), malignancy ($P = .737$), histopathologic subtype ($P = .464$), or grade of inflammation ($P = .209$); however, it showed a slight association with recurrence ($P = .06$). Notably, patients with a high Ki-67 index had significantly higher ALK expression ($P = .036$).

Patients with both high-grade ALK and inflammation showed a worse prognosis

Until October 2017, the median follow-up time was 21 months (range 2−116 months). In total, there were 18 deaths, of which 13 resulted from an IMT-related cause. Five patients died as a result of pulmonary infection. The Kaplan-Meier analysis predicted a 5-year OS rate of 60.8% and a 5-year DFS rate of 51%. A total of 23 patients (45.1%) had recurrence during the follow-up; of these, 11 patients had recurrence 2 times, and 2 patients had recurrence 3 times. Two patients had lymph node metastases, and 2 patients had distant metastases.

The Kaplan-Meier analysis and the log-rank test revealed that patients with high-grade ALK expression had worse DFS compared with those in the low-grade group ($P = .045$; Figure 2). There was no significant difference between patients with high-grade inflammation and those with low-grade inflammation with regard to DFS ($P = .286$; Figure 3). Notably, patients with both high-grade ALK expression and inflammation had worse DFS ($P = .008$; Figure 4). The group with high-grade ALK expression and inflammation had worse OS, although the difference was not statistically significant ($P = .088$).

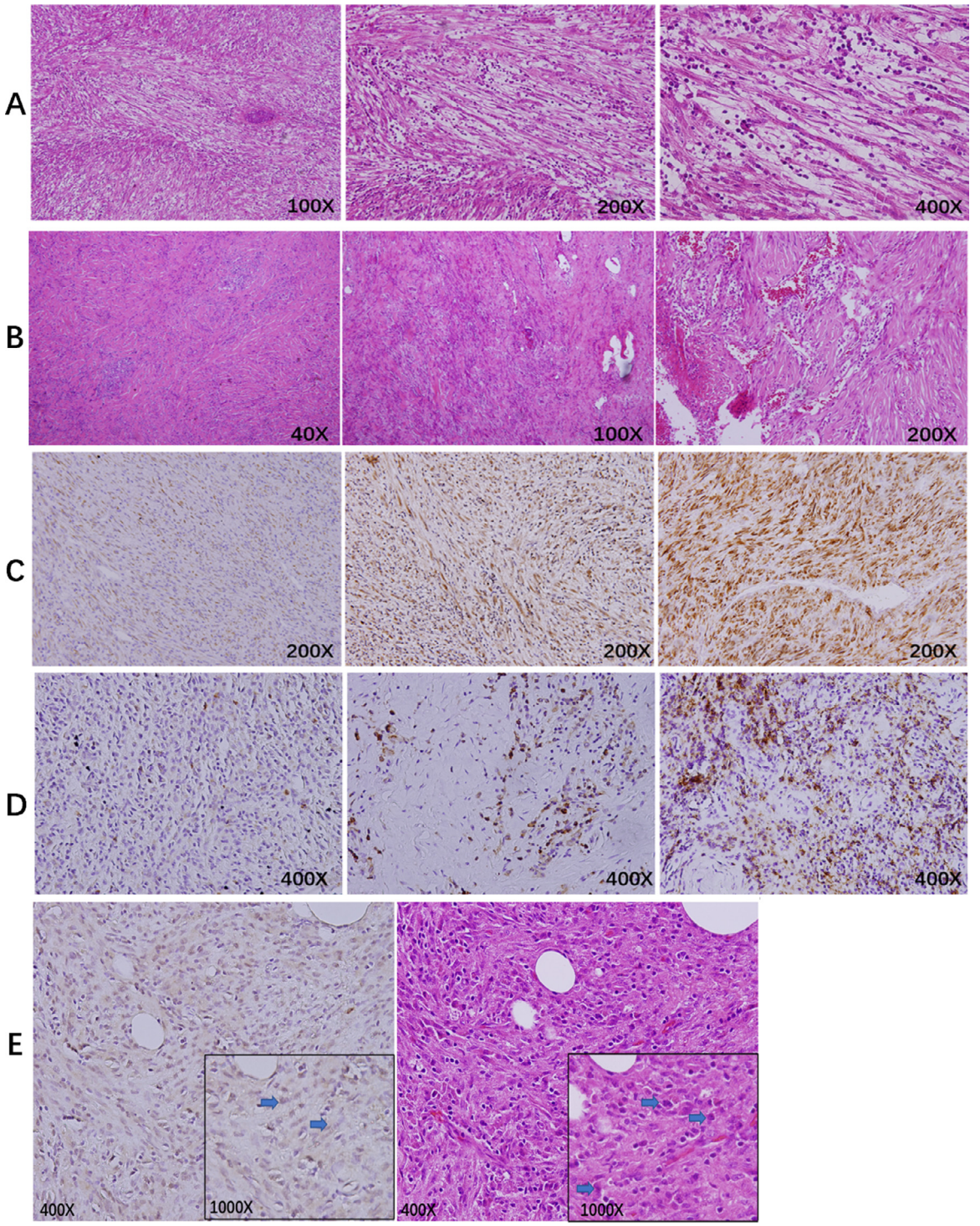

Fig. 1. Representative pathologic images of inflammatory myofibroblastic tumor (IMT). **A**, Representative hematoxylin and eosin (H&E)−stained images of inflammatory myofibroblastic tumor in the head and neck (HNIMT) under different microscope powers. **B**, Representative images of different inflammation degrees (*from left to right:* high, medium, low). **C**, Representative images of different anaplastic lymphoma kinase (ALK) degrees (*from left to right:* high, low, medium, high). **D**, Representative images of different cyclooxygenase-2 (COX-2) degrees (*from left to right:* low, medium, high). **E**, Representative images of HNIMTs with malignant transformation in a low ALK stain (blue arrows show tumor cells with cytologically atypical form and aberrant mitosis).

Table II. Correlation between ALK expression and clinicopathologic feature

Variable	*No. (%)*	*ALK expression*		*P value*
		High	*Low*	
Gender				.330
Male	15 (34.1%)	5	10	
Female	26 (59.1%)	14	12	
Recurrence				.060
Yes	15 (59.1%)	10	5	
No	26 (34.1%)	9	17	
Malignant				.737
Yes	13 (31.7%)	7	6	
No	28 (68.3%)	12	16	
Histopathologic subtypes				.464
Myxoid	9 (22.0%)	4	5	
Compact	8 (19.5%)	3	5	
Hyalinized	24 (58.5%)	15	9	
Grade of inflammation				.209
High	39 (95.1%)	17	22	
Low	2 (4.9%)	2	0	
Ki-67 index				.036*
High	15 (46.9%)	12	3	
Low	17 (53.1%)	7	10	

ALK, anaplastic lymphoma kinase.
*P < 0.05.

The grades of ALK expression and inflammation were independent risk factors for DFS

According to the univariate Cox analysis, gender, age, histologic subtype, degrees, grade of inflammation, grade of ALK expression, necrosis, Ki-67 index, and radiotherapy history did not significantly influence DFS or OS, as shown in Table III. In addition, tumors greater than 4 cm in size (DFS, $P = .016$; OS, $P = .011$); those located over the ala-tragus line (DFS, $P = .016$; OS, $P = .023$); tumors with both high-grade inflammation and ALK expression (DFS, $P = .015$; OS, $P = .104$); and tumors with malignant transformation (DFS, $P = .010$; OS, $P = .001$) had worse DFS and OS, according to the log-rank test. For the multivariate Cox analysis, grades of ALK expression and inflammation ($P = .004$) and tumor size ($P = .042$) were independent risk factors for DFS, whereas patients with tumors with malignant transformation ($P = .011$) had worse OS (see Table III).

DISCUSSION

Our results showed that most HNIMTs (66.7%) had a moderate or severe degree of inflammation with a lack of spindle cells. It has been indicated that in different kinds of tumors, inflammation has a close relationship with tumorigenesis, growth, and metastasis.[15] On average, HNIMTs have a higher degree of inflammation than those in other sites, and this is attributed to HNIMTs' location adjacent to the upper aerodigestive tract and the abundance of lymphatic tissue. Among an abundance of inflammatory factors, COX-2 may play a pivotal role. A widely held view about the carcinogenic mechanism of

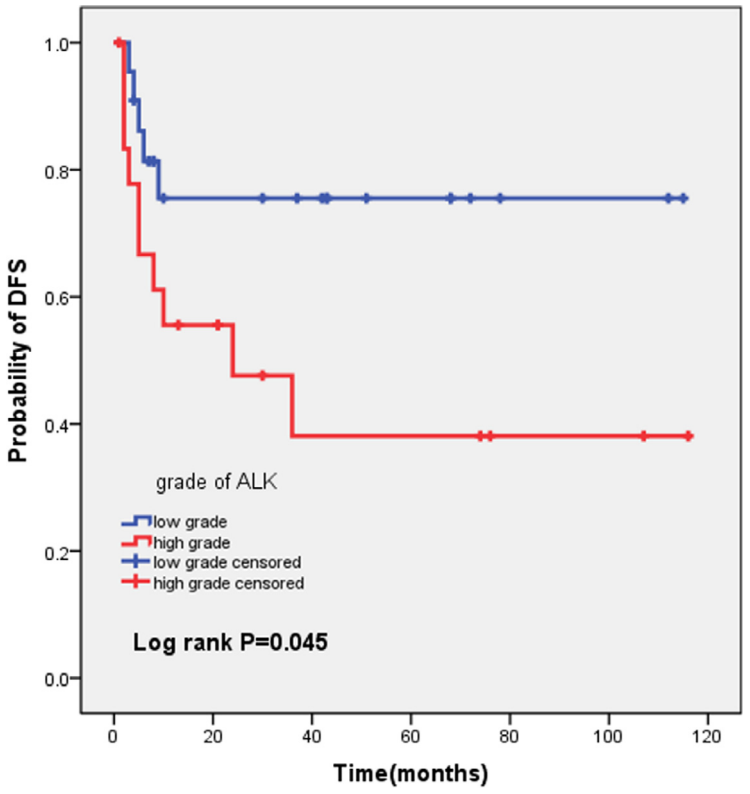

Fig. 2. Kaplan-Meier survival curve for anaplastic lymphoma kinase (ALK) grades and disease-free survival (DFS) time according to different ALK grades.

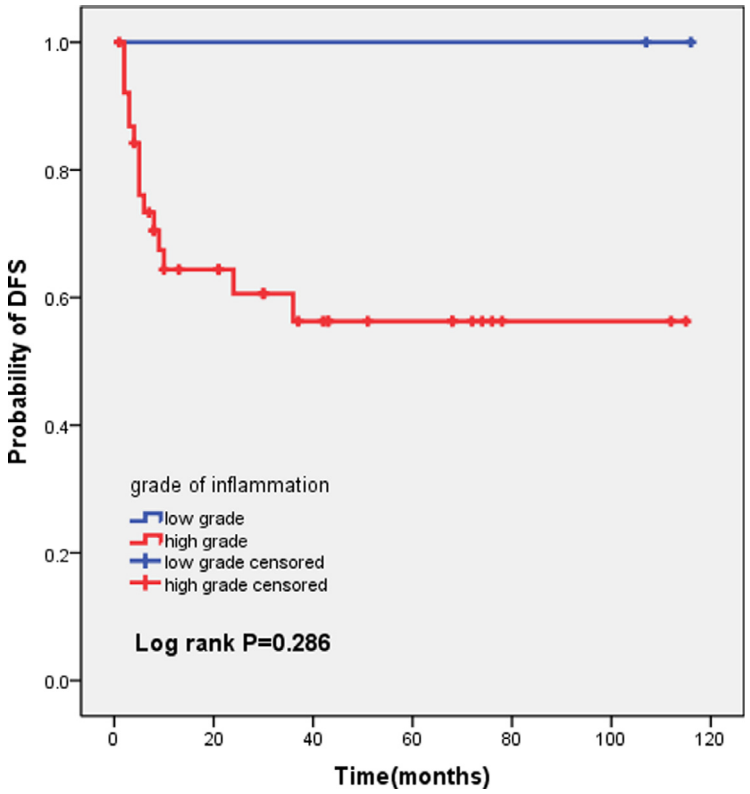

Fig. 3. Kaplan-Meier survival curve for inflammation and disease-free survival (DFS) time according to different inflammation grades.

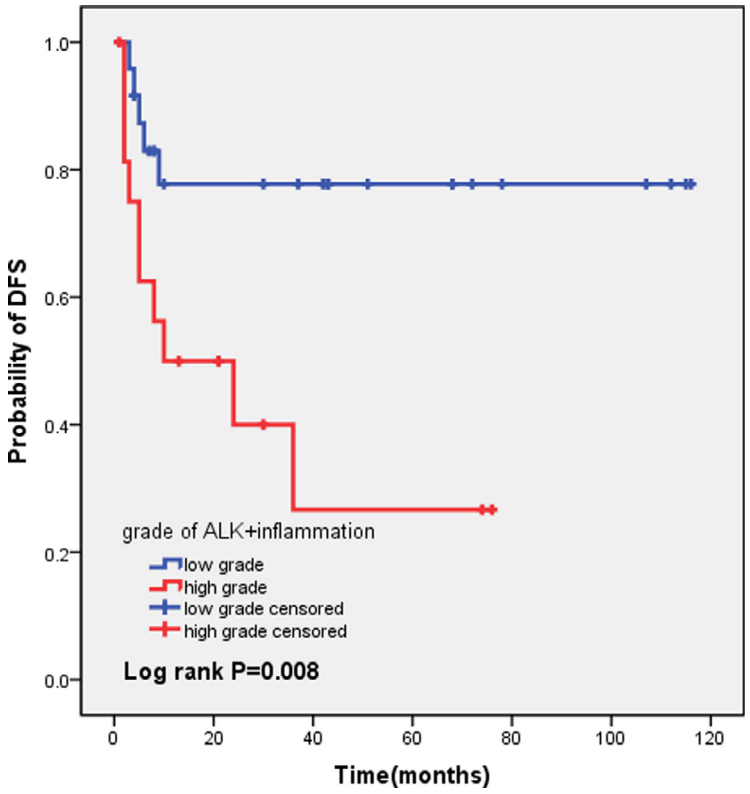

Fig. 4. Kaplan-Meier survival curve for grades of anaplastic lymphoma kinase (ALK) expression and inflammation and disease-free survival (DFS) time according to different grades of ALK expression and inflammation.

Table III. Univariate analysis and multivariate analysis for the estimation of risk factors for the DFS and OS in patients with head and neck IMT

Variable	*Hazard ratio*	*95% confidence interval*	*P value*
Univariate analysis for DFS			
Gender	0.848	0.362−1.985	.704
Age	1.368	0.592−3.158	.463
Tumor size	3.823	1.284−11.381	.016*
Site	3.085	1.237−7.692	.016*
Histologic subtype	0.369	0.128−1.063	.139
Grade of inflammation	22.625	–	.491
Grade of ALK	2.824	0.962−8.262	.059
Grade of ALK and inflammation	3.836	1.299−11.330	.015*
Necrosis	1.339	0.375−4.779	.652
Malignancy	3.104	1.31−7.353	.010*
Ki-67 index	3.301		.060
Radiotherapy history	1.075	0.459−2.519	.868
Multivariate analysis for DFS			
Grade of ALK and inflammation	5.002	1.649−15.173	.004*
Tumor size	3.416	1.048−11.133	.042*
Univariate analysis for OS			
Gender	0.719	0.283−1.823	.487
Age	1.045	0.410−2.660	.927
Tumor size	13.732	1.824−103.397	.011*
Site	3.349	1.183−9.476	.023*
Histologic subtype	0.314	0.075−1.321	.186
Grade of inflammation	22.43	–	.56
Grade of ALK	2.103	0.614−7.200	.236
Grade of ALK and inflammation	2.782	0.811−9.541	.104
Necrosis	1.848	0.489−6.981	.365
Malignancy	6.143	2.169−17.394	.001*
Ki-67 index	4.572		.069
Radiotherapy history	0.641	0.239−1.718	.377
Multivariate analysis for OS			
Malignant	4.993	1.450−17.187	.011*

ALK, anaplastic lymphoma kinase; DFS, disease-free survival; OS, overall survival.
*P < 0.05.

COX-2 is that it promotes cell proliferation, inhibits cell apoptosis, and accelerates angiogenesis.[16-18] The overexpression of COX-2 has already been proven to be related to the development of prostate cancer, breast cancer, liver cancer, and sclerosing fibroma.[19] Different intracellular signaling pathways can induce COX-2 expression by activating nuclear factor−κB, and the overexpression of COX-2 can enhance its activity in return, reducing the expression of E-cadherin and resulting in tumor invasiveness.[16,20,21] Therefore, we hypothesized that inflammatory factors, especially COX-2, might cause tumor invasion in HNIMT.

ALK is a widely accepted tumor marker of IMTs. Physiologically, ALK is expressed at low levels in the central nervous system, contributing to its development and functional coordination.[22,23] Pathologically, *ALK* is an oncogene that results in the aberrant expression of ALK.[24] By activating the signal transduction pathways for cell proliferation and cytoskeletal rearrangement, such as Ras/ERK, JAK/STAT, PI3 K/Akt, and PLC γ, abnormal proliferation and tumorigenesis are induced.[23,25] It has also been reported that aberrant expression of ALK exists in approximately 50% of IMTs. In an earlier study, Ong et al. used only 1 antibody, ALK-1, and the positive rate was 37.5% in 28 samples.[3] In this study, we optimized the strategy by using 4 antibodies (ALK-1, ALK-SP8, ALK-DF53, and ALK-1A4), thus achieving a 51.2% positive rate, similar to those reported in other studies. Nevertheless, the prognostic value of ALK for HNIMT remains controversial. It has been reported that high ALK expression is related to a high recurrence rate, whereas low ALK expression reduces the rate of metastasis.[26,27] Our results showed that ALK alone did not significantly impact OS or DFS.

When taken together, patients with both high-grade ALK expression and inflammation had worse DFS and OS, and the grades of ALK and inflammation were independent risk factors for DFS. The hazard ratio model implied a synergistic effect of ALK and inflammation in the tumorigenesis and development of HNIMTs. Studies on ALK-positive anaplastic large cell lymphoma have shown that ALK-positive tumor cells release HMGB-1 (high mobility group box 1) and MMP-9 (matrix metallopeptidase-9) and then activate protease-activated receptors, thus causing keratinocytes to release different kinds of cytokines and chemotactic factors and eventually causing inflammation.[20,21,28] In addition, inflammation promotes the invasive ability of tumor cells, as mentioned above. On the basis of the findings from our study and others, we concluded that ALK and inflammation have a synergistic effect on the tumorigenesis of HNIMTs.

Surgery remains the mainstay treatment of HNIMTs except for IMTs located in the orbital region, but multidisciplinary therapy has been widely applied in select cases.[9,29−31] According to our finding regarding synergistic effects in the tumorigenesis of HNIMTs, we propose that combined therapy with an ALK inhibitor and a COX-2 inhibitor might be effective to treat HNIMTs, especially those with high-grade ALK levels. However, cell and animal studies are necessary to verify this.

CONCLUSIONS

ALK and inflammation may have synergistic effects in the tumorigenesis of HNIMTs. Tumors with both high-

grade inflammation and ALK expression had a worse prognosis, and these variables were identified as independent risk factors for DFS. Combined use of ALK inhibitors and COX-2 inhibitors as adjuvant therapy offers significant promise in the treatment of HNIMTs.

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REFERENCES

1. Rosenberg AE. WHO Classification of Soft Tissue and Bone, fourth edition: Summary and commentary. *Curr Opin Oncol*. 2013;25:571-573.
2. Al-Humidi A, Al-Khamiss A. Inflammatory myofibroblastic tumor arising in the external ear: unexpected location. (case report). *Int J Health Sci (Qassim)*. 2015;9:201-205.
3. Ong HS, Ji T, Zhang CP, et al. Head and neck inflammatory myofibroblastic tumor (IMT): evaluation of clinicopathologic and prognostic features. *Oral Oncol*. 2012;48:141-148.
4. Coffin CM, Dehner LP, Meis-Kindblom JM. Inflammatory myofibroblastic tumor, inflammatory fibrosarcoma, and related lesions: an historical review with differential diagnostic considerations. *Semin Diagn Pathol*. 1998;15:102-110.
5. Meis-Kindblom JM, Kjellstrom C, Kindblom LG. Inflammatory fibrosarcoma: update, reappraisal, and perspective on its place in the spectrum of inflammatory myofibroblastic tumors. *Semin Diagn Pathol*. 1998;15:133-143.
6. Brunn H. Two interesting benign lung tumors of contradictory histopathology. *Am J Surg*. 1939;9:119-131.
7. Sciot R, Dal Cin P, Fletcher CD, et al. Inflammatory myofibroblastic tumor of bone: report of two cases with evidence of clonal chromosomal changes. *Am J Surg Pathol*. 1997;21:1166-1172.
8. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med*. 2010;363:1727-1733.
9. Kusunoki-Nakamoto F, Matsukawa T, Tanaka M, et al. Successful treatment of an unresectable inflammatory myofibroblastic tumor of the frontal bone using a cyclooxygenase-2 inhibitor and methotrexate. *Intern Med*. 2013;52:623-628.
10. Bennett JA, Nardi V, Rouzbahman M, Morales-Oyarvide V, Nielsen GP, Oliva E. Inflammatory myofibroblastic tumor of the uterus: a clinicopathological, immunohistochemical, and molecular analysis of 13 cases highlighting their broad morphologic spectrum. *Mod Pathol*. 2017;30:1489-1503.
11. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol*. 1997;15:350-362.
12. Marino-Enriquez A, Wang WL, Roy A, et al. Epithelioid inflammatory myofibroblastic sarcoma: an aggressive intra-abdominal variant of inflammatory myofibroblastic tumor with nuclear membrane or perinuclear ALK. *Am J Surg Pathol*. 2011;35:135-144.
13. Hutarew G, Hauser-Kronberger C, Strasser F, Llenos IC, Dietze O. Immunohistochemistry as a screening tool for ALK rearrangement in NSCLC: evaluation of five different ALK antibody clones and ALK FISH. *Histopathology*. 2014;65:398-407.
14. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. *J Cell Physiol*. 2000;182:311-322.
15. Affara NI, Coussens LM. IKKalpha at the crossroads of inflammation and metastasis. *Cell*. 2007;129:25-26.
16. Wang L, Kang F, Li J, Zhang J, Shan B. Overexpression of p65 attenuates celecoxib-induced cell death in MDA-MB-231 human breast cancer cell line. *Cancer Cell Int*. 2013;13:14.
17. Wang G, Li J, Zhang L, Huang S, Zhao X, Zhao X. Celecoxib induced apoptosis against different breast cancer cell lines by down-regulated NF-kappaB pathway. *Biochem Biophys Res Commun*. 2017;490:969-976.
18. Yang S, Wang X, Jiang H, Wang Y, Li Z, Lu H. Effective treatment of aggressive fibromatosis with celecoxib guided by genetic testing. *Cancer Biol Ther*. 2017;18:757-760.
19. de Moraes E, Dar NA, de Moura Gallo CV, Hainaut P. Cross-talks between cyclooxygenase-2 and tumor suppressor protein p53: balancing life and death during inflammatory stress and carcinogenesis. *Int J Cancer*. 2007;121:929-937.
20. Krawczyk M, Emerson BM. p50-associated COX-2 extragenic RNA (PACER) activates COX-2 gene expression by occluding repressive NF-kappaB complexes. *Elife*. 2014;3:e01776.
21. Zhai B, Yang H, Mancini A, He Q, Antoniou J, Di Battista JA. Leukotriene B(4) BLT receptor signaling regulates the level and stability of cyclooxygenase-2 (COX-2) mRNA through restricted activation of Ras/Raf/ERK/p42 AUF1 pathway. *J Biol Chem*. 2010;285:23568-23580.
22. Mano H. ALKoma: a cancer subtype with a shared target. *Cancer Discov*. 2012;2:495-502.
23. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. 1995;267:316-317.
24. Barreca A, Lasorsa E, Riera L, et al. Anaplastic lymphoma kinase in human cancer. *J Mol Endocrinol*. 2011;47:R11-R23.
25. Lin JJ, Riely GJ, Shaw AT. Targeting ALK: precision medicine takes on drug resistance. *Cancer Discov*. 2017;7:137-155.
26. Coffin CM, Patel A, Perkins S, Elenitoba-Johnson KS, Perlman E, Griffin CA. ALK1 and p80 expression and chromosomal rearrangements involving 2 p23 in inflammatory myofibroblastic tumor. *Mod Pathol*. 2001;14:569-576.
27. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. *Am J Surg Pathol*. 2007;31:509-520.
28. Li Q, Liu N, Shen B, et al. Helicobacter pylori enhances cyclooxygenase 2 expression via p38 MAPK/ATF-2 signaling pathway in MKN45 cells. *Cancer Lett*. 2009;278:97-103.
29. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med*. 2012;4(120):117-120.
30. Dzierba CD, Takvorian AG, Rafalski M, et al. Synthesis, structure-activity relationships, and in vivo properties of 3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-ones as corticotropin-releasing factor-1 receptor antagonists. *J Med Chem*. 2004;47(23):5783-5790.
31. Minoo P, Wang HY. ALK-immunoreactive neoplasms. *Int J Clin Exp Pathol*. 2012;5(5):397-410.

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