# Head and Neck Mesenchymal Tumors with Kinase Fusions

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# Head and Neck Mesenchymal Tumors with Kinase Fusions

## *A Report of 15 Cases With Emphasis on Wide Anatomic Distribution and Diverse Histologic Appearance*

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**Abstract:** Mesenchymal tumors harboring various kinase fusions were recently recognized as emerging entities mainly in the soft tissues. We herein investigate the clinicopathologic and molecular characteristics of head and neck mesenchymal tumors harboring kinase fusions. The study cohort included 15 patients with a median age of 13 years (ranging from congenital to 63 y). The kinase genes involved in descending order were *NTRK1* (n = 6), *NTRK3* (n = 5), *BRAF* (n = 2), and 1 each with *MET*, and *RET*. The anatomic locations were broad involving all tissue planes, including skin (n = 4), intraosseous (n = 4), major salivary glands (n = 2), sinonasal tract (n = 2), soft tissue of face or neck (n = 2), and oral cavity (n = 1). The histologic spectrum ranged from benign to high grade, in descending order including tumors resembling malignant peripheral nerve sheath tumor (MPNST)-like, fibrosarcoma (infantile or adult-type), lipofibromatosis-like neural tumor (LPFNT), inflammatory myofibroblastic tumor-like, and a novel phenotype resembling myxoma. Perivascular hyalinization/stromal keloid-like collagen bands and staghorn vasculature were common features in MPNST-like and LPFNT-like tumors. Two tumors (1 each with *NTRK1 or BRAF* rearrangement) were classified as high grade. By immunohistochemistry, S100 and CD34 positivity was noted in 71% and 60%, frequently in MPNST-like and LPFNT-like phenotypes. Pan-TRK was a sensitive marker for *NTRK*-translocated tumors but was negative in tumor with other kinase fusions. One patient with a high-grade tumor developed distant metastasis. Molecular testing for various kinase fusions should be considered for $S100^+/CD34^+$ spindle cell neoplasms with perivascular hyalinization and staghorn vessels, as pan-TRK positivity is seen only in *NTRK* fusions.

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Fusions involving kinase genes resulting in oncogenic activation of various protein kinases has been increasingly recognized in mesenchymal tumors. Fusion events have been reported to involve *NTRK1*, *NTRK2*, *NTRK3*, *BRAF*, *RAF1*, *RET*, *MET*, *EGFR*, *ROS1*, *ALK*, and *ABL1*.[1–3] In 1998, the canonical *ETV6::NTRK3* fusion was first described in the majority of infantile fibrosarcoma (IFS),[4,5] a tumor occurring mostly in infancy and being characterized by a primitive spindle cell fascicular proliferation often arranged in a distinctive herringbone pattern. Up to 10% of IFS occur in the head and neck (HN) region, with reported sites including scalp, dura, tongue, parotid, neck, and orbit.[6–9]

In 2016, Agaram et al[10] first described *NTRK1* fusions in lipofibromatosis-like neural tumors (LPFNT), a superficially located and highly infiltrative mesenchymal tumor characterized by short fascicles of bland spindle cells within mature adipose tissue, which are consistently $CD34^+$ and $S100^+$. Soon after, rearrangements involving other kinase genes, including *NTRK2*,[3,11] *NTRK3*,[3,12,13] *RET*,[14] *MET*,[3,15] *RAF1*,[11] *ROS1*,[3] *ALK*,[3] *ABL1*,[16] and *BRAF*,[11] were also documented in mesenchymal tumors with overlapping features. Based on the accumulated experience across various gene fusions, the histologic spectrum of kinase fusion-positive mesenchymal tumors has been expanded to include several emerging categories, including LPFNT, molecular subsets of IFS, tumors resembling malignant peripheral nerve sheath tumor (MPNST)-like, adult-type fibrosarcoma (FS)-like, inflammatory myofibroblastic tumor (IMT)-like, hemangiopericytoma/myopericytoma-like with prominent staghorn vasculature, or adenosarcoma-like described exclusively in uterine cervix and prostate.[1–3,10,11,14,17–20] It is important to recognize the histologic spectrum of these tumors so that appropriate immunohistochemistry and molecular testing can be initiated to detect the underlying fusions as these patients may be a candidate for targeted therapy using various kinase inhibitors.[21–24]

Although mesenchymal tumors with kinase fusion were first described in superficial soft tissues,[10] a wide range of anatomic sites, including deep soft tissue, thoracic cavity, gynecologic tract, and gastrointestinal tract, can be involved by these tumors.[3,19,20,25–29] The HN region can occasionally be affected, however, to date, merely 9 HN cases have been reported as single case reports or small series, including 7 with *NTRK1* fusion, and 1 each with *NTRK3* fusion, and *RET* fusion.[3,8,10,11,26,30] We herein describe the clinicopathologic features of a large cohort of 15 cases with HN mesenchymal tumors harboring kinase fusions, including 3 cases of IFS with canonical *ETV6::NTRK3* fusion, 1 IFS-like tumor with *RBPMS::MET* fusions, and 12 other mesenchymal tumors with *NTRK1*, *NTRK3*, *BRAF*, or *RET* gene rearrangements.

## MATERIALS AND METHODS

### Patients' Selection and Clinicopathologic Review

The study was approved by the Institutional Review Board (IRB) of Memorial Sloan Kettering Cancer Center (MSKCC). Candidate cases were retrieved from the pathology archives of MSKCC and the personal consultation cases of one of the authors (C.R.A.) based on the presence of kinase gene fusion or rearrangement as documented by molecular studies (fluorescence in situ hybridization [FISH] or targeted RNA sequencing). All identified HN mesenchymal tumors with kinase fusions were included in this study. All cases were reviewed by 2 pathologists (B.X. and C.R.A.) to gather relevant pathologic parameters (architectural pattern, presence of lipofibromatosis-like component, cytomorphology, nuclear pleomorphism, mitotic activity, necrosis) demographic, and outcome data. IMT cases with typical morphology and *ALK or ROS1* fusions were excluded from the study. Each tumor was further subdivided into IFS, IFS-like tumor, tumor with overlapping features of LPFNT, MPNST-like, Adult FS-like, IMT-like, and myxoma-like based on their histologic features, immunoprofile, and underlying fusion using definitions provided in Table 1.

Immunohistochemistry studies were reviewed for the following primary antibodies: S100 (polyclonal, dilution: 1:8000, DAKO; Agilent), CD34 (clone: QBEnd-10, ready to use [RTU], Ventana; Roche Diagnostics), SOX10 (clone: BC34, dilution: 1:50; Biocare Medical), smooth muscle actin (SMA, clone: 1A4, dilution 1:200; Cell Marque Corporation), desmin (clone: DE.R.11, RTU, Ventana, Roche Diagnostics), myogenin (clone: FSD, RTU, Cell Marque; Sigma-Aldrich), and pan-TRK (clone EPR17341, dilution 1:100; Abcam).

### Targeted RNA Sequencing and FISH Detection of Kinase Fusions

Kinase fusions were detected in all cases using targeted RNA sequencing (n = 6) and/or FISH (n = 11). In brief, targeted RNA sequencing was performed using an anchored multiplex polymerase chain reaction–based clinical molecular diagnostic assay (MSK-Archer FusionPlex) in a CLIA-accredited laboratory, to detect oncogenic fusion transcripts including a panel of 123 genes.[31] FISH analyses for kinase genes (*NTRK1*, *NTRK3*, *RET*, *MET*, and *BRAF*) and fusion partners (*ETV6*, *LMNA*, *TPR*, and *TPM3*) was performed using custom bacterial artificial chromosome clone probes designed to flank the target genes based on the UCSC genome browser (http://genome.ucsc.edu/) as previously described.[3,10,11,13]

## RESULTS

A total of 15 cases with confirmed kinase fusions originating from the HN region were selected. Three patients with *LMNA::NTRK1* fusion-positive tumors were reported previously by our group.[3,10,11] The clinicopathologic features, immunoprofile, clinical outcome, and underlying fusion events are summarized in Table 2.

### Clinical Features

The median age of presentation was 13 years (range from 0 wk [at birth] to 63 y). Among them, IFSs and IFS-like tumors were only diagnosed during infancy (0 to 6 wk). There was no gender predilection (female to male ratio of 1:1.14). The sites of involvement showed a wide distribution, including dermis and subcutis (n = 4, 1 from face and neck and 3 from scalp), intraosseous (n = 4, 2 from skull base, 1 from maxilla, and 1 from mandible), major salivary glands (n = 2, 1 each from submandibular and parotid gland), sinonasal tract (n = 2, 1 each from frontal sinus and nasal cavity), deep soft tissue (n = 2, 1 each from face and neck), and oral cavity (n = 1, upper gingiva).

**TABLE 1.** Definition of Histologic/Immunohistochemical Subcategories of Mesenchymal Tumors With Kinase Fusions

| Categories | Definitions |
|---|---|
| IFS | Primitive spindle/ovoid/round cell tumors, often with fascicular/herringbone arrangement, occurring in patients <2 y, harboring the cannonical *ETV6::NTRK3* fusion |
| IFS-like tumor | IFS phenotype as defined above, with alternative kinase fusions other than *ETV6::NTRK3* |
| LPFNT | Tumor with monotonous bland spindle cells showing a highly infiltrative pattern within adjacent adipose tissue at the periphery, frequent S100 and CD34 positivity, prominent stromal collagen deposit, and perivascular hyalinization |
| MPNST-like | $S100^{+}$ cellular spindle cell tumors showing exclusive solid architecture, frequent stromal collagen deposits, and perivascular hyalinization |
| Adult-type FS-like | $S100^{-}$ cellular spindle cell tumors showing exclusive solid architecture, often with fascicular/herringbone arrangement, occurring in patients $\geq 2$ y |
| IMT-like | $S100^{-}$ plump/ovoid neoplasm heavily infiltrated by mixed inflammatory cells. In this study, conventional IMTs with *ALK* or *ROS1* rearrangement are excluded |
| Myxoma-like | Hypocellular hypovascular myxoid neoplasm with bland stellate to spindle cells |

## Molecular Findings

The kinase genes affected were *NTRK1* (n = 6), *NTRK3* (n = 5), *BRAF* (n = 2), *MET* (n = 1), and *RET* (N = 1).

Kinase fusions were detected by Archer FusionPlex in 5 cases (cases #1, #4, #13 to #15) showing in-frame gene products including the kinase domain. The transcript gene fusions were between *ETV6* exon 5 and *NTRK3* exon 15 (n = 2, cases #1 and #14); between *KIAA1549* exon 13 and *BRAF* exon 11 (case #13); between *KIF5B* exon 24 and *RET* exon 11 (case #15); and between *RBPMS* exon 5 and *MET* exon 15 (case #4).

The remaining cases were confirmed to have kinase gene rearrangements by FISH as well as their partners in 6 cases, including *LMNA::NTRK1* (n = 2), *TPR::NTRK1* (n = 1), *TPM3::NRK1* (n = 1), and *ETV6::NTRK3* (n = 2).

## Histologic Features and Immunoprofile

All tumors were subclassified based on their histologic features and immunoprofile into different morphologic phenotypes, including IFS (n = 4), LPFNT (n = 3), MPNST-like (n = 4), adult FS-like (n = 2), IMT-like (n = 1), and myxoma-like (n = 1). The histologic features were diverse and did not appear to correlate with the type of underlying fusions.

In addition to the malignant phenotype displayed by the 4 IFS tumors, there were 2 other tumors that showed features in keeping with a high-grade sarcoma, based on nuclear atypia, elevated mitotic index of $\geq 10$ per 10 HPFs, and tumor necrosis, including 1 MPNST-like with *NTRK1* rearrangement (case #11) and an adult FS-like with *KIAA1549::BRAF* fusions (case #13).

### Infantile Fibrosarcomas

There were 4 cases in this cohort which had a FS phenotype and occurred in infants. Three of the cases showed the canonical *ETV6::NTRK3* fusion (cases #1 to #3) and were in keeping with the classic IFS entity, while 1 case showed the presence of a *RBPMS::MET* fusion and was considered a molecular variant of IFS (or IFS-like, case #4). The greatest dimension of the tumors ranged from 3 to 9 cm (median: 5.1 cm), which was significantly larger than the remaining tumors (median: 1.7 cm, range: 0.8 to 4.7 cm, 2-tailed Student *t* test, $P = 0.017$). Histologically, all cases showed hypercellular solid growth either arranged in intersecting fascicles with the prototypical herringbone pattern or as sheets of ovoid cells forming ill-formed fascicles (Fig. 1). The tumors had a monomorphic appearance with scant cytoplasm and uniform ovoid nuclei. Staghorn (hemangiopericytoma-like) vasculature was noted in all except 1 case. Mitotic index was highly variable, ranging from 1 to 30 mitotic figures (MFs) per 10 HPFs. Tumor necrosis and nuclear atypia with prominent nucleoli was seen in 1 case (case #1, *NTRK3::ETV6* fusion). None of the IFSs showed perivascular hyalinization, dense hyalinized collagen bands, or areas reminiscent of lipofibromatosis.

Pan-TRK immunostain was performed in an IFS with *ETV6::NTRK3* fusion which showed weak cytoplasmic immunopositivity. Focal S100 and SMA immunopositivity were seen in 1 case, respectively (S100: case #2, *ETV6::NTRK3* fusion; SMA: case #4, *RBPMS::MET* fusion). All cases examined were negative for CD34 (n = 3), desmin (n = 3), and myogenin (n = 3).

### Lipofibromatosis-like Neural Tumor

Three tumors (cases #5 to #7) had a hybrid morphology with areas of LPFNT component intermixed with solid growth. The LPFNT component was typically noted at the periphery of the solid areas, accounting for 5% to 30% of total tumor volume. None of the lesions showed a pure LPFNT morphology. The solid component was centrally located and was composed of a uniform but hypercellular growth (Fig. 2A), resembling a low-grade peripheral nerve sheath tumor, with a low mitotic count (1 to 5 MFs/10 HPFs) and no necrosis. The LPFNT component was hypocellular and highly infiltrative, composed of short fascicles of the bland spindle to ovoid cells within adipose tissue (Fig. 2B). Prominent ring-like perivascular hyalinization, keloid-type thick collagen bundles, and staghorn vasculature were seen in 2 cases each in the solid area (Figs. 2C, D).

Among the cases with immunohistochemistry performed, this group of tumors showed a $CD34^+$ (n = 2), $S100^+$ (n = 2), and $SOX10^-$ (n = 1) results. Two of these lesions showed *NTRK1* fusions. The fusion partners were *LMNA* in 1 case and not examined in the other. The third case showed *BRAF* rearrangement. Pan-TRK was performed on 1 tumor with *NTRK1* rearrangement and showed diffuse cytoplasmic immunopositivity.

### MPNST-like Tumors

In 4 cases (cases #8 to #11), the tumor was entirely solid and showed features resembling MPNST, composed of primitive uniform ovoid cells with scant cytoplasm arranged in a vague fascicular pattern (Fig. 2E). Perivascular hyalinization and stromal collagen bands were common, being seen in all except 1 case. Two patients had staghorn vasculature. In this group, a scalp tumor harboring *NTRK1* rearrangement in a 30-year-old patient (case #10) showed high-grade features with a mitotic index of 20/10 HPFs, tumor necrosis, and nuclear atypia. MPNST-like tumors were inevitably positive for S100 (Fig. 2F). CD34 immunopositivity was also common, being seen in 3 cases (75%, Fig. 2G). Pan-TRK immunostain was performed in 2 cases, including a *NTRK1*-translocated and a *NTRK3*-translocated tumor showing cytoplasmic positivity (Fig. 2H). The fusion events were all involving *NTRK* genes, including *LMNA::NTRK1* fusion, *TPM3::NTRK1* fusion, *NTRK1* rearrangement, and *NTRK3* rearrangement, respectively.

### Adult-type FS

Cases #12 and #13 were composed of fascicles of monotonous spindle cells arranged in a herringbone pattern, resembling adult-type FS (Figs. 2I, J). One case

**TABLE 2.** Clinical, Pathologic, and Molecular Features of HN Mesenchymal Tumors With Kinase Fusions

| Case # | Age/Sex | Location | Anatomic Levels | Kinase Genes With Fusion | Fusion Partners | Size (cm) | MI | Necrosis | Nuclear Atypia |
|---|---|---|---|---|---|---|---|---|---|
| IFS (n = 3) | | | | | | | | | |
| 1 | 0 wk/F | Face/neck | Dermis/ subcutis | *NTRK3* | *ETV6* | 9 | 30 | Y | Y |
| 2 | 2 wk/F | Neck | ST | *NTRK3* | *ETV6* | 3 | 7 | N | N |
| 3 | 6 wk/M | Submandibular | Salivary | *NTRK3* | *ETV6* | 4 | 6 | N | N |
| IFS-like tumor (n = 1) | | | | | | | | | |
| 4 | 4 wk/F | Face | ST | *MET* | *RBPMS* | 6.3 | 1 | N | N |
| Tumor with overlapping features of LPFNT (N = 3) | | | | | | | | | |
| 5 | 4 y/M | Mandible | Bone and ST | *NTRK1* | *LMNA* | 4 | 5 | N | N |
| 6 | 38 y/F | Scalp | Dermis/ subcutis | *NTRK1* | NA | 2.8 | 1 | N | N |
| 7 | 14 y/M | Frontal sinus | Sinonasal tract | *BRAF* | NA | 0.8 | 0 | N | N |
| MPNST-like (n = 4) | | | | | | | | | |
| 8 | 13 y/M | Maxilla | Bone | *NTRK1* | *LMNA* | NA | 0 | N | N |
| 9 | 18 y/M | Nasal cavity | Sinonasal tract | *NTRK1* | *TPM3* | 1 | 0 | N | N |
| 10 | 30 y/M | Scalp | Dermis/ subcutis | *NTRK1* | NA | 1.8 | 20 | Y | Y |
| 11 | 63 y/F | Upper gingiva | Oral cavity | *NTRK3* | NA | 1.4 | 3 | N | N |
| Adult-type FS-like (n = 3) | | | | | | | | | |
| 12 | 2 y/F | Scalp | Dermis/ subcutis | *NTRK1* | *TPR* | 2 | 8 | N | N |
| 13 | 22 y/F | Parotid | Salivary | *BRAF* | *KIAA1549* | 5 | 10 | Y | Y |
| IMT-like (n = 1) | | | | | | | | | |
| 14 | 9 wk/M | Skull base | Bone and ST | *NTRK3* | *ETV6* | 4.7 | 3 | N | N |
| Myxoma-like (n = 1) | | | | | | | | | |
| 15 | 15 y/M | Skull base | Bone | *RET* | *KIF5B* | 1.3 | 0 | N | N |

− indicates negative; +, positive; AWD, alive with disease; C, cytoplasmic; DM, distant metastasis; F, female; LR, local recurrence; M, male; MI, mitotic index (per 10 HPFs); N, no; NA, not available; NED, no evidence of disease; ST, soft tissue; Y, yes.

(case #13) was high grade with nuclear atypia, high mitotic index, and tumor necrosis. CD34 and S100 were negative in this group. The underlying fusions of these tumors were *TPR::NTRK1* and *KIAA1549::BRAF*.

## Rare Histotypes Included Tumors Resembling IMT and Myxoma

Case #15, a 9-week-old boy presenting with a skull base lesion, showed histologic features reminiscent of an IMT. The tumor involved bone and extended in soft tissue and was predominantly hemorrhagic and cystic (Figs. 3A, B). The solid areas within the cystic wall were composed of plump to ovoid cells arranged in syncytial sheets, heavily infiltrated by a mixed inflammatory infiltrate of lymphocytes, histiocytes, plasma cells, and eosinophils. The tumor showed occasional MFs and was negative for CD34 and S100. Pan-TRK immunostain showed cytoplasmic positivity. Archer FusionPlex showed the presence of an *ETV6::NTRK3* fusion.

Case #16, an intraosseous skull base tumor arising in a 15-year-old boy, showed an unusual hypocellular, hypovascular myxoid appearance indistinguishable from a myxoma (Figs. 3C, D). It was composed entirely of bland stellate and spindle cells in a myxoid background. There was no mitotic activity, cytologic atypia, or tumor necrosis. The initial histologic diagnosis of this case was an intraosseous myxoma. By Archer FusionPlex the tumor revealed a *KIF5B::RET* fusion.

## Pan-TRK Immunostaining

Pan-TRK immunostain was performed in 6 cases, including 2 with *NTRK1* fusion, 3 with *NTRK3* fusion, and 1 with *RET* fusion, and was positive with cytoplasmic staining in 5 cases with *NTRK1/3* fusion (Figs. 1D, 2H, 3, inset) and negative in the case with *RET* fusion. No nuclear immunopositivity was seen in this cohort.

## Clinical Outcome

Clinical outcome was available in 4 cases with a follow-up period of 7 to 648 months (median: 82 mo). A 30-year-old male patient with a high-grade *NTRK1*-translocated scalp tumor showing adult-type FS-like histology developed distant metastasis to chest wall and was alive with disease at the last follow-up 7 months after the diagnosis.

In addition, an infant with congenital IFS harboring *ETV6::NTRK3* fusion that was resected with no gross residual disease, but microscopically positive margin developed distant metastasis to brain and bone and local recurrence. She was treated with multiple courses of chemotherapy (vincristine/actinomycin-D/cyclophosphamide; ifosfamide/doxorubicin, and ifosfamide/etoposide) with

**TABLE 2.** *Continued*

| Staghorn Vessels | Perivascular Hyalinization | S100 | CD34 | SOX10 | Pan-TRK (location) | DM | LR | Outcome |
|---|---|---|---|---|---|---|---|---|
| IFS (n = 3) | | | | | | | | |
| N | N | − | − | NA | + (C) | Y | Y | AWD (21 mo) |
| Y | N | + | − | NA | NA | NA | NA | NA |
| Y | N | NA | NA | NA | NA | NA | NA | NA |
| IFS-like tumor (n = 1) | | | | | | | | |
| Y | N | − | − | NA | NA | NA | NA | NA |
| Tumor with overlapping features of LPFNT (N = 3) | | | | | | | | |
| Y | N | + | + | NA | NA | N | Y | NED (142 mo) |
| Y | Y | + | + | − | + (C) | NA | NA | NA |
| N | Y | NA | NA | NA | NA | NA | NA | NA |
| MPNST-like (n = 4) | | | | | | | | |
| N | Y | + | + | − | NA | N | N | NED (648 mo) |
| Y | Y | + | + | NA | NA | NA | NA | NA |
| N | N | + | − | NA | + (C) | Y | N | AWD (7 mo) |
| Y | Y | + | + | NA | + (C) | NA | NA | NA |
| Adult-type FS-like (n = 3) | | | | | | | | |
| Y | Y | − | + | NA | NA | NA | NA | NA |
| Y | N | − | − | NA | NA | NA | NA | NA |
| IMT-like (n = 1) | | | | | | | | |
| Y | N | − | − | NA | + (C) | NA | NA | NA |
| Myxoma-like (n = 1) | | | | | | | | |
| N | N | − | − | NA | − | NA | NA | NA |



disease progression. She then received first-generation NTRK inhibitor larotrectinib with a partial response but later developed resistance. MSK-IMPACT next-generation sequencing on local recurrence showed a *NTRK3* G623R mutation, likely causing the drug resistance. She was alive with the disease at 21 months.

Last, a 4-year-old boy with *LMNA::NTRK1* fusion and an LPFNT histology developed late local recurrence 126 months after the initial resection. The recurrence was resected, and the patient was alive and disease free at 146 months.

## DISCUSSION

A major breakthrough in the classification of soft tissue tumors has been the recent identification of *NTRK* fusion-related neoplasms which have opened new avenues for targeted therapy. As a result, *NTRK*-rearranged spindle cell neoplasms have been recognized as an emerging diagnostic entity in the latest fifth edition of the World Health Organization (WHO) classification for soft tissue and bone tumors.[32] One of the first series by Agaram et al[10] described a group of tumors occurring with predilection in the superficial soft tissues in children and young adults which resembled lipofibromatosis, but showed a neural immunophenotype, with coexpression of S100 and CD34. Based on these distinct features a provisional terminology of LPFNT was used. Most of these tumors harbored *NTRK1* fusions with various partners, being immunopositive for pan-TRK, and followed a benign clinical course lacking metastatic potential. However, the spectrum of morphologies was soon expanded to include additional phenotypes resembling MPNST[11,13,14] or adult-type FS.[13,14,33–35] In fact, most of the $S100^{+}$ hypercellular solid lesions have been previously misdiagnosed as MPNST, although they typically lack SOX10 and do not occur in the setting of a preexistent neurofibroma or type I neurofibromatosis 1.[3,11,13,14] Moreover, it was further recognized that kinase fusion-positive tumors may display hybrid features, with alternating solid components and lipofibromatosis-like areas with a similar immunoprofile.[3,10,14,30] Less common histotypes including lesions resembling myopericytoma or IMT have been reported in few cases.[8,13,18,36] Aside from the common soft tissue sites, small series of tumors arising from the uterus[19,34,37] and prostate[20] have been described, including lesions that exhibit unique features such as adenosarcoma-like pattern.[19,20] In the gynecological locations, tumors recapitulating adenosarcoma[19] or FS[34,35] morphologies were documented, but other site-specific series of kinase positive mesenchymal neoplasms have not been investigated. In addition to this histologic heterogeneity, it became apparent that these lesions are driven by diverse kinase fusions in addition to the more common *NTRK1* and *NTRK3*, such as *NTRK2*,[3,11] *RET*,[14] *MET*,[3,15] *RAF1*,[11] *ROS1*,[3] *ABL1*,[16] *ALK*,[3] and *BRAF*.[11] Based on the overlapping histologic

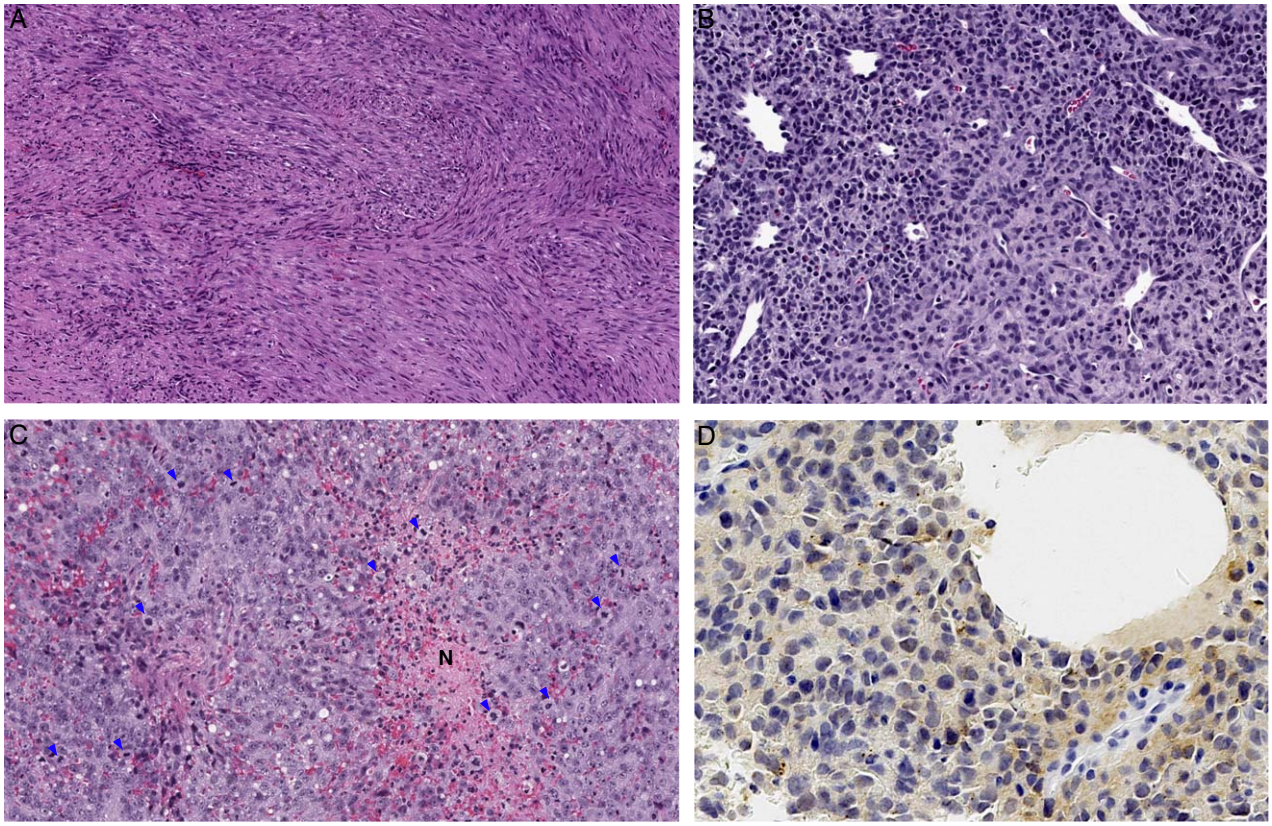


**FIGURE 1.** IFS in the HN region. A, An IFS-like neoplasm with *RBPMS::MET* fusion originated from the facial soft tissue showing the fascicular arrangement of bland spindle cells in a herringbone pattern (case #4). B, An IFS contains bland ovoid cells arranged in loose fascicles with staghorn (hemangiopericytoma-like) vasculature (case #3). C and D, This IFS of a newborn baby (case #1) shows ovoid cells with enlarged nuclei and prominent nucleoli, brisk mitotic activity (blue arrowheads), and focal tumor necrosis (N). Weak cytoplasmic positivity is noted on pan-TRK immunostain (D).

features and immunoprofile of these tumors with kinase fusions, consideration may be given to expand the WHO emerging entity *NTRK*-rearranged spindle cell neoplasms to spindle cell neoplasms with kinase fusions.

To date (including 11 cases from the current study), 17 patients with HN mesenchymal tumors harboring kinase fusions were reported in the literature after excluding IMT, IFS, and IFS-like tumors. The fusion events, clinicopathologic features, and immunoprofile of these cases are summarized in Table 3.[3,8,10,11,26,30] In the HN region, these tumors most frequently occur in teenagers and young adults, although a wide age range from 9 weeks to 63 years has been reported. The median age of presentation is 18 years. Such propensity for teenagers and young adults and wide age distribution are similar to what have been reported for mesenchymal tumors with kinase fusions from all body sites (median age: 12 to 21 y, range: 0 to 77 y).[3,13,26]

Within the HN region, the anatomic distribution of mesenchymal tumors with kinase tumors is ubiquitous, involving all tissue planes, including skin, bone (skull base, maxilla, and mandible), major salivary glands (parotid and submandibular glands), sinonasal tract, deep soft tissue of face and neck, and oral cavity. Therefore, these tumors should be considered in the differential diagnoses of a HN mesenchymal tumors.

Similar to the wide spectrum of histologic features reported in soft tissue sites, HN mesenchymal tumors with kinase fusions also exhibit morphologic diversity. The histologic patterns being observed in our cohort and previously reported HN cases in a descending frequency are MPNST-like, LPFNT, adult-type FS-like, IMT-like, and myopericytoma/hemangiopericytoma-like.[3,8,10,11,26,30] In addition, we herein reported a novel histologic appearance of hypocellular hypovascular myxoid tumor with *KIF5B::RET* fusion which is composed entirely of bland stellated cells resembling myxoma (ie, myxoma-like), hence expanding the histopathologic spectrum of mesenchymal tumors with kinase fusions. Adenosarcoma-like pattern, a feature described exclusively in gynecologic tract and prostate, is not seen in the HN region.[19,20] Characteristic histologic features being repeatedly observed in mesenchymal tumors with kinase fusions of soft tissue, especially in those with a MPNST-like appearance or those with overlapping features of LPFNT, include perivascular hyalinization, keloid-like hyalinizing collagen bands, and staghorn (hemangiopericytoma-like) vasculature.[1,3,9,11,13] Similarly, these features were common findings in our HN cohort.

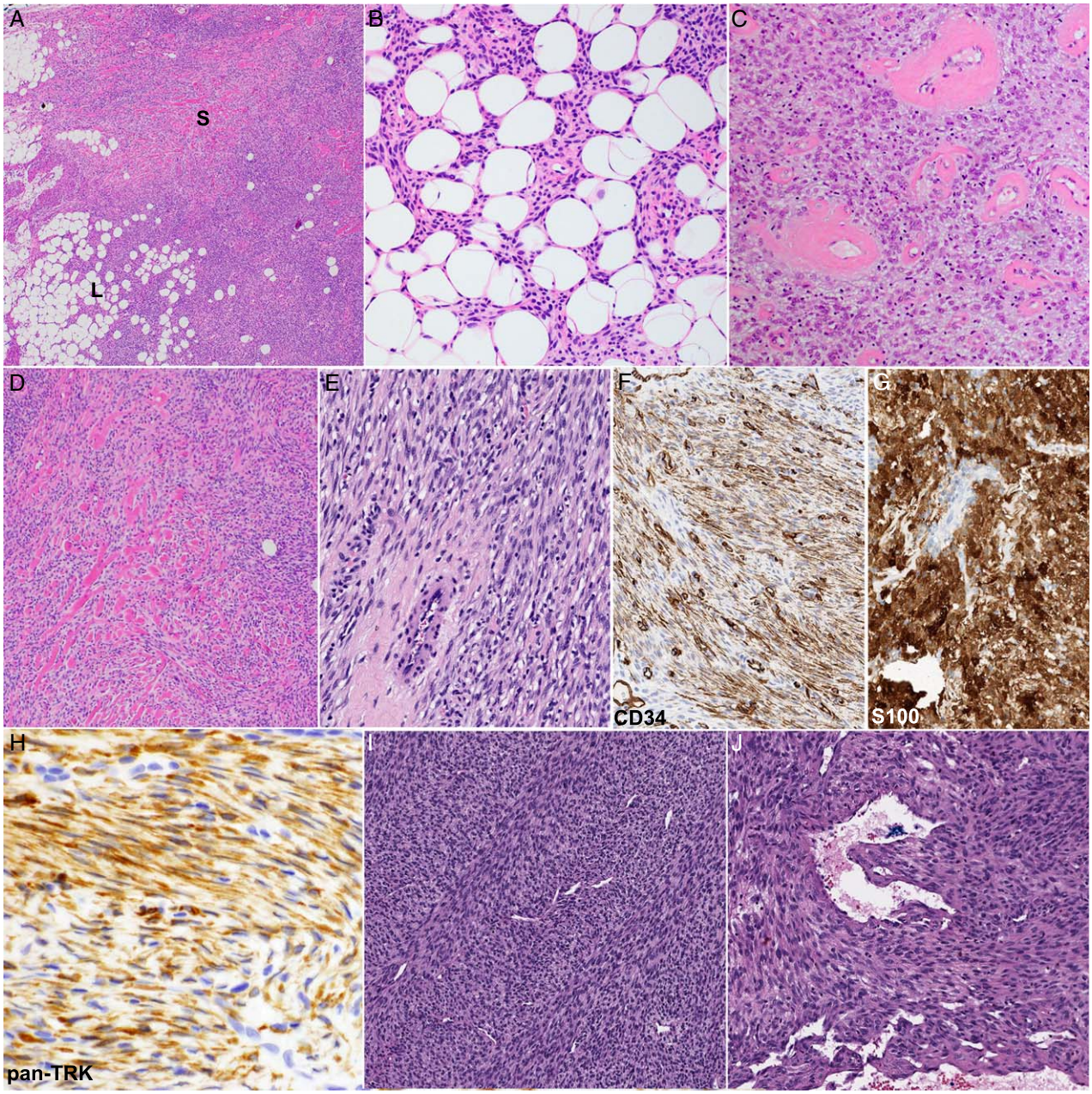


**FIGURE 2.** Mesenchymal tumors with kinase fusion: LPFNT, MPNST-like, and adult-type FS-like patterns. A and D, A scalp tumor with *NTRK1* fusion (case #6) is composed of a peripheral zone resembling LPFNT (L) and a central zone of solid growth (S). At higher power, the peripheral zone is composed of short fascicles of the bland spindle to ovoid cells infiltrating adipose tissue (B). The central zone resembles MPNST and is composed of sheets of bland spindle cells arranged in ill-formed fascicles. Marked perivascular hyalinization (C) and dense keloid-like fibrosis (D) are frequent findings. E–H, Case #11, an MPNST-like tumor with *NTRK3* fusion. The tumor cells form loose fascicles. Perivascular hyalinization is present. The tumor is positive for CD34 (F), S100 (G), and pan-TRK (cytoplasmic staining, H). I and J, Case #14 shows an adult-type FS-like pattern with fascicles of spindle cells arranged in a herringbone pattern (I). Branching staghorn (hemangiopericytoma-like) vessels is seen in this tumor (J).

The immunoprofile of tumors with kinase fusion vary according to histologic patterns. While most of the LPFNT-like and MPNST-like tumors are $CD34^+$, $S100^+$, but $SOX10^-$,[1,3,11,13] those resembling IMT and adult-type FS are $CD34^-$/$S100^-$/$SOX10^-$. Data from our HN series also support such observation. Overall, S100 and CD34 immunopositivity has been reported in 71% and 60%, respectively in all reported HN mesenchymal tumors with kinase fusions. With the exception of a single case of $S100^+$/$CD34^+$ IMT-like tumor with *NTRK3* rearrangement,[28] S100 and CD34 positivity are exclusively seen in LPFNT-like and MPNST-like tumors in the HN region.

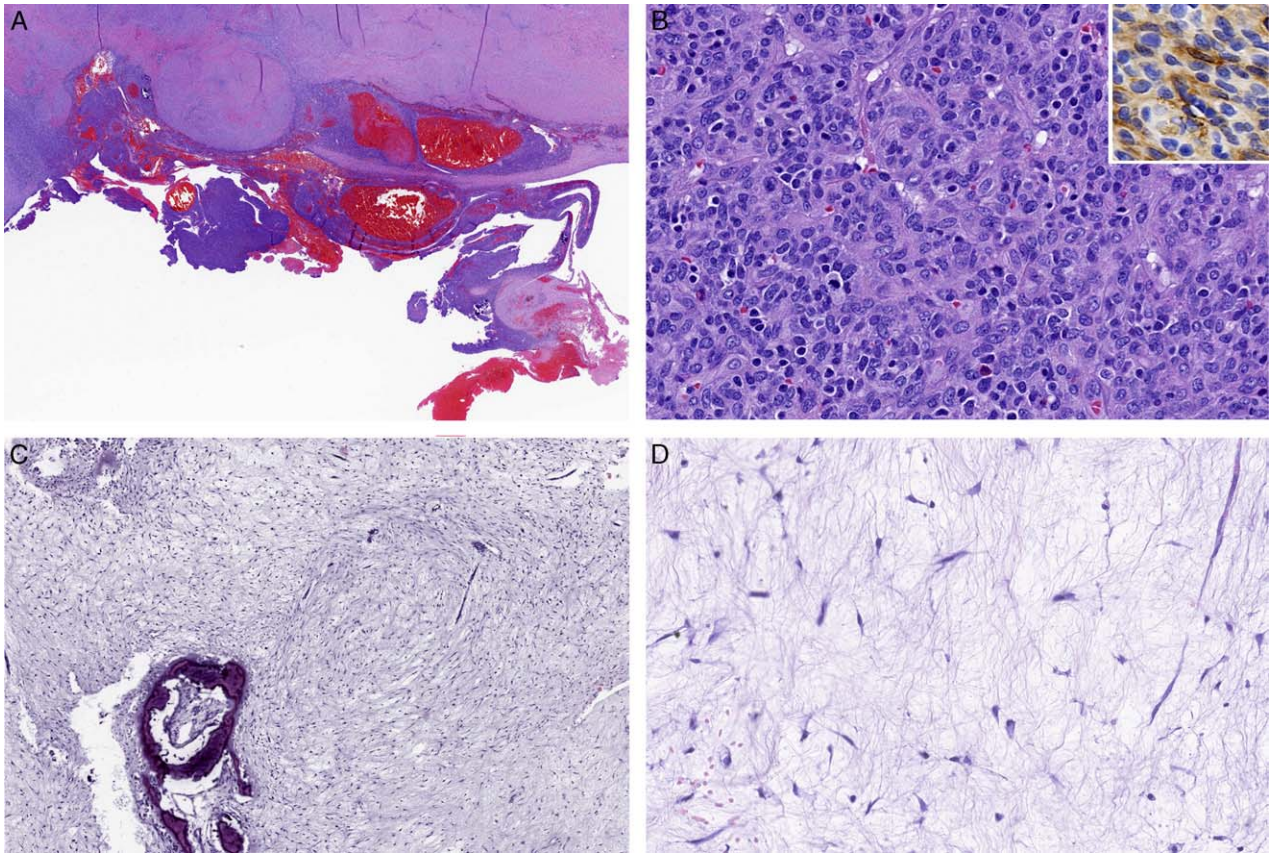


**FIGURE 3.** Mesenchymal tumors with kinase fusions displaying rare histologic patterns resembling IMT and myxoma. A and B, A skull base tumor with *ETV6::NTRK3* fusion is cystic and hemorrhagic. The solid areas contain oval to plump tumor cells arranged in a vague syncytial pattern heavily infiltrated by mixed inflammatory cells, including lymphocytes, histiocytes, plasma cells, and eosinophils. Inset: pan-TRK immunostain shows cytoplasmic positivity. C and D, An intraosseous hypocellular hypovascular myxoid tumor of the skull base with *KIF5B::RET* fusion resembling myxoma histologically (case #16). The tumor is composed of bland stellate cells in an abundant myxoid background.

Akin to mesenchymal tumors with kinase fusions from other body sites,[1,2] the most frequently rearranged kinases in the HN region remain to be *NTRK1* (n = 10/17, 59%) and *NTRK3* (n = 3, 18%). Other less common fusion kinases in the HN regions are *BRAF* (n = 2, 12%), *RET* (n = 2, 12%).

The differential diagnoses of these tumors in the HN region are broad mostly due to various histologic appearances of these tumors and a wide range of anatomic location. (Myo)fibroblastic tumors and peripheral nerve sheath tumors are the main groups of diagnostic mimickers, including entities such as neurofibroma, MPNST, IMT, solitary fibrous tumor, adult-type FS, glomangiopericytoma of sinonasal tract, and dermatofibrosarcoma protuberans. Our series described the first case of myxoma-like lesion. Therefore, myxoma also becomes a differential diagnosis. Given the diverse spectrum of histologic appearance and the wide distribution of mesenchymal tumors with kinase fusions in the HN region, one should have a low threshold to initiate appropriate tests for kinase fusions when facing unclassifiable HN spindle cell neoplasms, especially those with perivascular hyalinization, stromal dense collagen bands, staghorn vasculature, and $CD34^{+}/S100^{+}/SOX10^{-}$ immunoprofile. Meanwhile, it is important to stress that a negative S100 and CD34 immunoprofile does not exclude mesenchymal tumors with kinase fusions.

Pan-TRK immunohistochemistry has been initially proposed as a sensitive and specific screening test for underlying *NTRK* fusions regardless of tumor types.[38,39] However, several caveats have emerged when using pan-TRK immunohistochemistry to screen mesenchymal tumors with kinase fusions. First, pan-TRK immunohistochemistry is not entirely specific.[40] False positivity has been reported in various other sarcomas, including BCOR sarcoma,[20,41] undifferentiated uterine sarcoma,[20] Ewing sarcoma,[41] leiomyosarcoma,[26] synovial sarcoma,[26] extraskeletal myxoid chondrosarcoma,[26] liposarcoma,[26] and myxofibrosarcoma.[26] A recent study tested 2669 solid tumors with a low probability (< 1%) of *NTRK* fusions and showed that only 10% of pan-$TRK^{+}$ tumors harbored NTRK fusions.[42] Second, the sensitivity of pan-TRK immunohistochemistry has been reported in the range of 75% to 88% and is even lower in detecting *NTRK3* fusion.[38,40,43] Such a sensitivity implies

that 12% to 25% of tumors with *NTRK* fusions can be missed when using pan-TRK immunohistochemistry as a stand-alone test. Last, pan-TRK immunohistochemistry cannot detect kinase translocations other than *NTRK* family of genes. Therefore, although immunohistochemistry studies may serve as a cheap and rapid screening tool, more comprehensive molecular tests to including other kinase fusions are needed especially if the clinical suspicion is high based on histologic features and immunoprofile.

In practice, spindle cell neoplasms with kinase fusions should be considered as a differential diagnosis of HN spindle cell lesions, regardless of their anatomic locations, especially when facing: (1) mesenchymal tumors in children or young adults; (2) a histologic appearance of monotonous spindle cell proliferation forming short fascicles or patternless pattern, either infiltrating adipose tissue (resembling LPFNT) or forming hypercellular solid areas (resembling MPNST or adult-type FS), often with stromal collagen deposits and perivascular hyalinization; and (3) an immunoprofile of $S100^{+}/CD34^{+}/SOX10^{-}$. However, as the histology and immunophenotype may vary, a low threshold for subsequent testing is advised. Pan-TRK immunohistochemistry may serve as a rapid and cheap screening diagnostic tools for tumors with *NTRK* fusions. Definite diagnosis for this entity requires comprehensive molecular tests to cover all candidate kinase genes. For a more in-depth comprehensive discussion of the diagnostic approach for soft tissue tumors with kinase fusions, see a recent review by Antonescu.[1]

Detection of kinase fusions in these tumors is essential not only for diagnostic purpose but also for determination of eligibility for tyrosine kinase inhibitor therapy. Recently, TRK inhibitors, larotrectinib, and entrectinib, have been approved by the Food and Drug Administration (FDA) to treat advanced or metastatic *NTRK*-rearranged cancers, including sarcoma.[44] Other tyrosine kinase inhibitors are also used in treating mesenchymal tumors with kinase fusions in clinical trials.[45]

One limitation of the current study was the lack of follow-up data in most of the cases as a significant number were consultation cases. Among the 3 non-IFS cases with follow-up data available, only 1 high-grade tumor with elevated mitotic activity and tumor necrosis developed distant metastasis, supporting the previous observation that the prognosis of these tumors is related to histologic grade and that high-grade tumors may spread distantly.[1,2,13]

Our study also included 3 cases of IFS and 1 case of IFS-like tumor with *RBPMS::MET* fusion from the HN region. In the WHO classification fifth editions, IFS with

**TABLE 3.** Literature Review: HN Mesenchymal Tumors With Kinase Fusions

| References | Kinase Fusions | Anatomic Site | Age (y) | Sex | MI/ Necrosis | Histologic Features | S100 | CD34 | Pan-TRK | DM | LR | Outcome (FU period) (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | *LMNA::NTRK1* | Neck (subcutis) | 50 | M | NA/NA | LPFNT | + | + | +C | N | N | NED (20) |
| 8 | *LMNA-NTRK1* | Forehead (dermis/subcutis) | 3 | M | 0/N | NA | + | + | +NM | N | N | NED (9.6) |
| 11* | *LMNA::NTRK1* | Mandible (bone/soft tissue) | 4 | M | 5/N | LPFNT | + | + | NA | N | Y | NED (142) |
| 11* | *LMNA::NTRK1* | Maxilla (bone) | 13 | M | 0/N | MPNST-like | + | + | NA | N | N | NED (648) |
| 28 | *TPM3::NTRK1* | Neck (soft tissue) | 53 | F | NA/Y | MPNST-like | − | − | +C | N | Y | DOD (24) |
| 18 | *TPM3::NTRK1* | Supraclavicular (soft tissue) | 51 | F | 16/NA | Myopericytoma/HPC-like | NA | − | NA | N | N | NED (29) |
| * | *TPM3::NTRK1* | Nasal cavity (sinonasal tract) | 18 | M | 0/N | MPNST-like | + | + | NA | NA | NA | NA |
| * | *TPR::NTRK1* | Scalp (dermis/subcutis) | 2 | F | 8/N | FS-like | + | + | NA | NA | NA | NA |
| 3,10* | *NTRK1* | Scalp (dermis/subcutis) | 38 | F | 1/N | LPFNT | + | + | +C | NA | NA | NA |
| * | *NTRK1* | Scalp (dermis/subcutis) | 30 | M | 20/Y | MPNST-like | + | − | +C | Y | N | AWD (7) |
| * | *ETV6::NTRK3* | Skull base (bone and soft tissue) | 9 wk | M | 3/N | IMT-like | − | − | +C | NA | NA | NA |
| 28 | *NTRK3* | Forehead (subcutis) | 24 | F | 0/N | IMT-like | + | + | +C | N | N | NED (6) |
| * | *NTRK3* | Gingiva (mucosa) | 63 | F | 3/N | MPNST-like | + | + | +C | NA | NA | NA |
| * | *KIAA1549::BRAF* | Parotid (salivary gland) | 22 | F | 10/Y | FS-like | − | − | +C | NA | NA | NA |
| * | *BRAF* | Frontal sinus (sinonasal tract | 14 | M | 0/N | MPNST-like | NA | NA | NA | NA | NA | NA |
| 30 | *VCL::RET* | Neck (soft tissue) | 7 mo | M | NA/NA | LPFNT | NA | NA | NA | NA | NA | NA |
| * | *KIF5B::RET* | Skull base (bone) | 15 | M | 0/N | Myxoma-like | − | − | − | NA | NA | NA |

*This study.

Cases of IFS and infantile sarcoma-like lesion are excluded.

− indicates negative; +, positive; AWD, alive with disease; +C/N, positive (cytoplasmic and nuclear); +C, positive (cytoplasmic); DM, distant metastasis; DOD, dead of disease; F, female; FU, follow-up; HPC, hemangiopericytoma; +N, positive (nuclear); +NM, positive (nuclear and membranous); LR, local recurrence; M, male; MI, mitotic index (per 10 HPFs); N, no; NA, not available; NED, no evidence of disease; Y, yes.

canonical *ETV6::NTRK3* fusion and IFS-like tumors with alternative fusions involving *NTRK1*, *BRAF*, or *RET* genes were classified under the umbrella term of IFS.[32] *RBPMS::MET* fusion has only been previously reported in a single case of an IFS-like tumor presenting as a facial mass in a 1-month-old infant.[46] In our cohort, IFS occurred exclusively in infants 6-week-old or younger. In contrast, the reported HN tumors with kinase fusions occurred mostly in teenagers and adults. However, there are overlap between the 2 groups in term of age, histologic, immunochemical, and molecular features. It remains to be seen whether these tumors represent 2 ends of the same spectrum of tumors or 2 distinct entities with overlapping kinase fusions.[2]

In conclusion, mesenchymal tumors with kinase fusions may occur in a wide range of anatomic sites within the HN region. The most frequent fusion event involves the *NTRK1* gene, however, rearrangements of other kinase genes, such as *NTRK3*, *BRAF*, *RAF1*, *MET*, and *RET*, may also occur. The histologic patterns and grades are variable in these tumors, including a novel phenotype of hypocellular hypovascular myxoma-like appearance. Stromal and perivascular hyalinization, staghorn vessel, and CD34/S100 positivity are common findings, especially in tumors with histologic features resembling LPFNTs or MPNSTs. Although pan-TRK serves as a good screening tool, molecular testing to cover other kinase genes may be needed for accurate diagnosis and for selecting patients for kinase inhibitor therapy.

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