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Fetal Rhabdomyoma of the Larynx in an Adult

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Significant Statement

Fetal rhabdomyoma (FRM) is an uncommon benign soft tissue tumor showing skeletal muscle differentiation. It occurs predominantly in the head and neck region of infants and young children. We describe an adult patient presenting with dysphonia and cough for a polypoid glottic FRM in which a *SUFU* gene deletion was found by molecular analysis. When dealing with a laryngeal polypoid lesion in an adult, FRM should be kept in mind as a very rare diagnosis.

Rhabdomyoma is a benign soft tissue neoplasm showing skeletal muscle differentiation.[1,2] Three subtypes (ie, fetal, adult, and genital) are distinguished. The fetal subtype is the rarest, occurs predominantly in the head and neck of infants and young children and in approximately 25% of cases is congenital.[1,2] Less than 30 cases of FRM have been reported in patients older than 20 years.[3] Even though fetal rhabdomyoma (FRM) is usually sporadic, it may also occur in association with nevoid basal cell carcinoma syndrome,[4-6] a genetic syndrome associated with monoallelic loss-of-function germline mutations of hedgehog signaling pathway (HHSP)-related genes, especially *PTCH1* (OMIM #109400) and *SUFU* (OMIM #620343).[7,8] Notably, mutations of HHSP-related genes have been reported also in sporadic FRMs.[6,9]

Histologically, FRM has been distinguished into 2 variants (classic/myxoid and juvenile/cellular) based on the degree of cellularity, amount of myxoid stroma, and maturity of muscle cells; however, this distinction does not affect the prognosis and the 2 histologic variants frequently coexist blending into each other.[1,2]

We report here the case of a 31-year-old man presenting at the othorhinolaryngology clinic for a 5 months history of dysphonia and cough. He denied smoking history and previous laryngeal surgery. A flexible transnasal pharyngo-laryngoscopy showed a nonulcerated polypoid lesion involving the glottis (Figure 1A). The polyp disappeared in subglottis with inspiration and appeared in supraglottis with expiration and was interpreted as benign even though a specific diagnosis was not made. It was excised with a carbon dioxide laser. Pathologic examination revealed a soft, unencapsulated, and paucicellular polypoid lesion composed of primitive spindle cells and more differentiated skeletal muscle fibers dispersed in a loose stroma (Figure 1B and C). Mitosis, atypia, necrosis, and a "cambium layer" were absent. Immunohistochemical analysis, performed as described previously,[10,11] showed immunoreactivity of both neoplastic cell components for desmin (Figure 1D). The more differentiated skeletal muscle fibers were also immunoreactive for myoglobin. The proliferation index (Ki-67) was less than 5%. Based on these findings, the diagnosis of classic FRM was made. The postoperative course was unremarkable and recurrences were not

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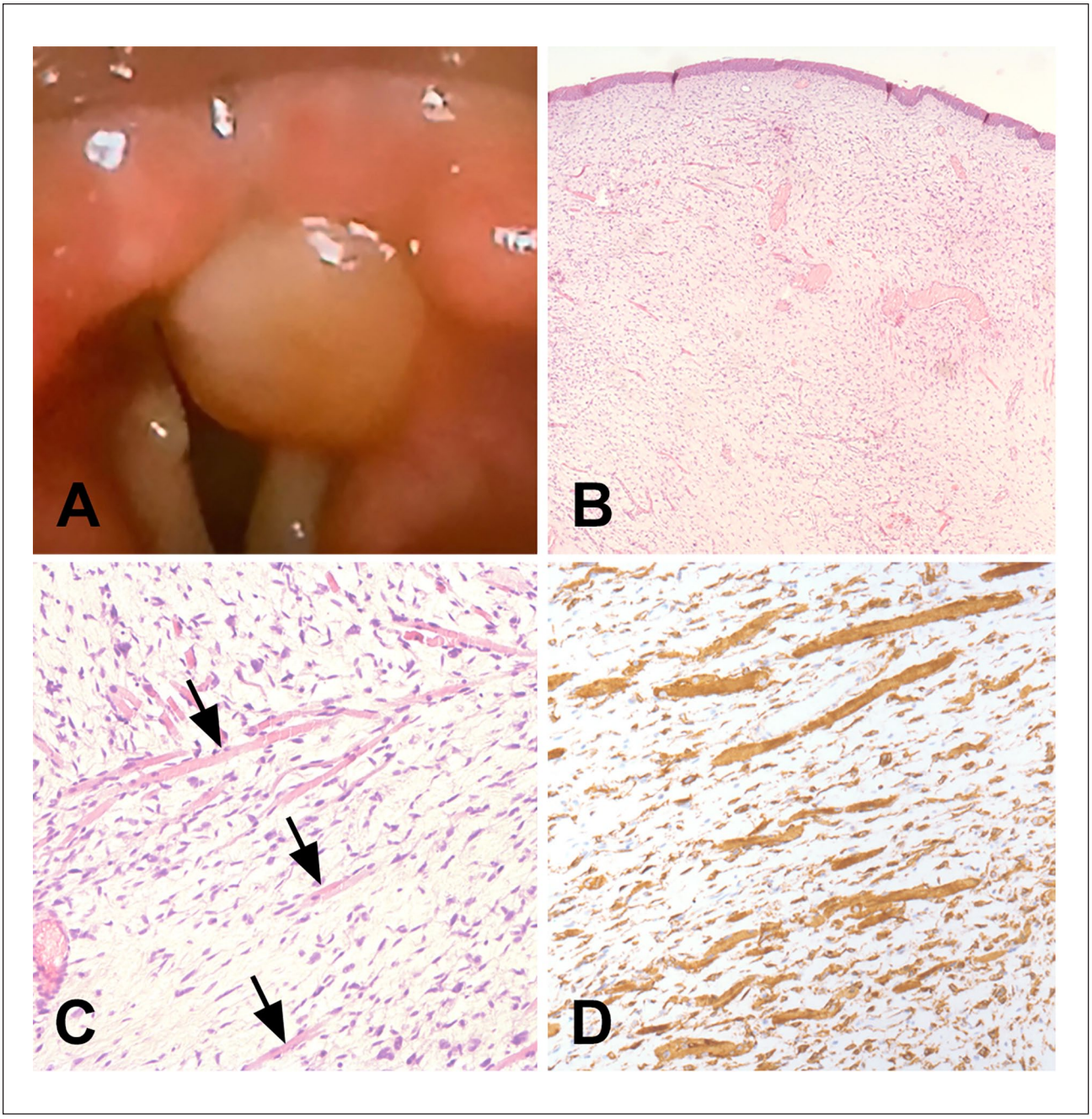
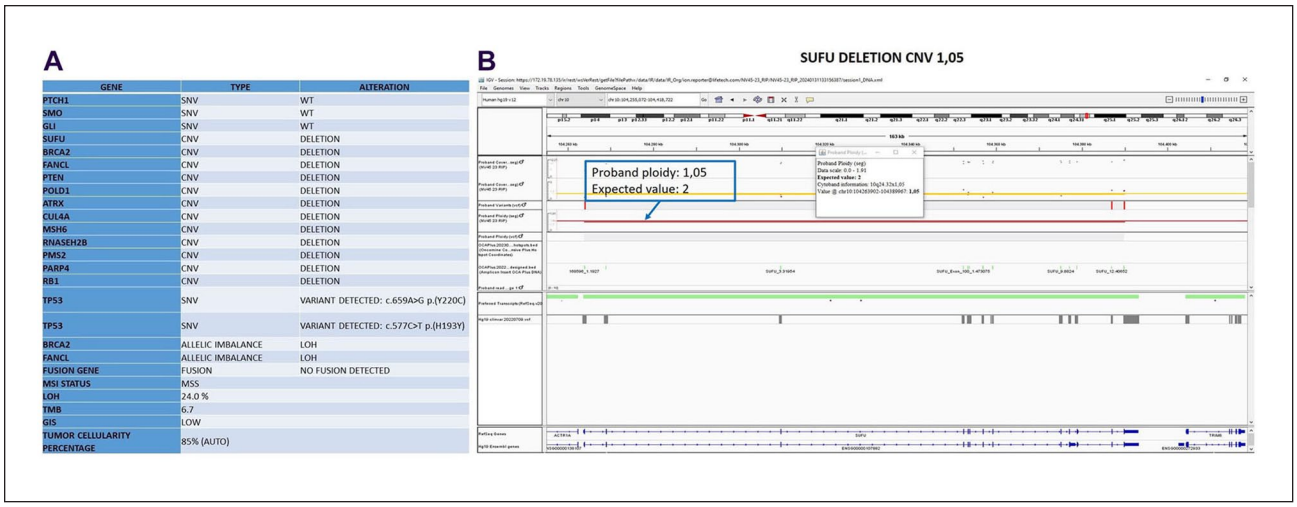


Figure 1. Clinical presentation and low- and high-power magnification of the glottic polypoid lesion are illustrated in A, B (hematoxylin-eosin, 10× magnification), and C (hematoxylin-eosin, 40× magnification), respectively. In C, more differentiated skeletal muscle fibers are identified by arrows. Desmin immunoreactivity of both primitive spindle cells and more differentiated skeletal muscle fibers is illustrated in D (40× magnification).

appreciated for 10 months after surgery. Molecular analysis was also performed on genomic DNA and RNA extracted from paraffin sections. Next-generation sequencing (Ion Torrent, IonGene Studio™ S5 Prime System, Thermo Fisher Scientific) using the Oncomine Comprehensive Assay Plus (OCA+, Thermo Fisher



GENE	TYPE	ALTERATION
PTCH1	SNV	WT
SMO	SNV	WT
GLI	SNV	WT
SUFU	CNV	DELETION
BRCA2	CNV	DELETION
FANCL	CNV	DELETION
PTEN	CNV	DELETION
POLD1	CNV	DELETION
ATRX	CNV	DELETION
CUL4A	CNV	DELETION
MSH6	CNV	DELETION
RNASEH2B	CNV	DELETION
PMS2	CNV	DELETION
PARP4	CNV	DELETION
RB1	CNV	DELETION
TP53	SNV	VARIANT DETECTED: c.659A>G p.(Y220C)
TP53	SNV	VARIANT DETECTED: c.577C>T p.(H193Y)
BRCA2	ALLELIC IMBALANCE	LOH
FANCL	ALLELIC IMBALANCE	LOH
FUSION GENE	FUSION	NO FUSION DETECTED
MSI STATUS	MSS	
LOH	24.0 %	
TMB	6.7	
GIS	LOW	
TUMOR CELLULARITY PERCENTAGE	85% (AUTO)	

Figure 2. (A) Genetic alterations identified through NGS Oncomine Comprehensive Assay Plus panel. SNV, Single Nucleotidic Variants; CNV, Copy Number Variation; LOH, Loss of Heterozygosity; MSI, Microsatellite Instability; MSS, Microsatellite Stable; TMB, Tumor Mutational Burden; GIS, Genomic Instability Status. (B) Representation of *SUFU* gene deletion on Integrative Genomics Viewer (IGV, https://www.igv.org/). The panel shows the chromosomal region of the patient (chr10: 104263902-104389967) and its ploidy level compared to the wildtype. This region includes the *SUFU* gene. Since ploidy refers to the number of copies of each chromosome, we would expect to see 2 copies of each chromosome (diploidy) in a normal sample. In the case of a deletion, a lack or reduction in signal intensity in the affected region will be evident. In our case, the reduction in chromosome copy number in the affected region indicates a lower-than-normal ploidy; and therefore, it appears consistent with loss of signal due to deletion of *SUFU* gene.

Scientific) detected a deletion in the *SUFU* gene (chr10: 104263902-104389967) that encodes a key negative regulator of HHSP.[7] Additional alterations were identified in other genes including *BRCA2* and *TP53* but not in other genes associated with the HHSP including *PTCH1*, *SMO*, and *GLI1* (Figure 2). The Reactome pathway database was also employed to ascertain the pathways or biological processes associated with the identified altered genes.[12] Notably, processes predominantly linked to DNA repair mechanisms were identified (Figure 3). Based on these results, molecular testing on peripheral blood was recommended to assess for germline alterations.

Otolaryngologists might not be familiar with FRM because development of this tumor in the upper airways is extremely rare.[3,12,13] A recent review of the literature revealed that only 8 cases of FRM have been reported in the larynx of adult patients.[13] Clinical presentation is not specific. Hoarseness, airway obstruction, and inspiratory stridor are the most common chief complaints.[13] The spectrum of clinical differential diagnosis is huge including cysts and benign (eg, granular cell tumor) and malignant (eg, rhabdomyosarcoma) tumors. Only histological and immunohistochemical analysis let the diagnosis definitely. However, FRM may cause diagnostic challenge due to its morphologic resemblance to embryonal rhabdomyosarcoma from which it can be distinguished, as in the case presented here, for the superficial location and the lack of invasion of adjacent tissue, significant nuclear atypia, infiltrative growth, necrosis, and atypical mitosis.[1,2] Its radical surgical excision is commonly curative. Indeed, recurrences have been reported rarely.[8,14] A follow-up of at least 1 year after surgery has been suggested[15] even though FRM may recur years after the initial diagnosis.[14] In our case, the demonstration of a *SUFU* gene deletion confirms that deregulation of HHSP plays a role in the pathogenesis of at least a subset of sporadic FRM.[6,9] To date, alterations of genes related to the HHSP have never been reported in FRM involving the larynx. Nevertheless, when dealing with a laryngeal polypoid lesion in an adult, FRM should be kept in mind by otolaryngologists as a very rare diagnosis.

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
DNA Repair	7 / 380	0.025	8.47e-08	2.46e-05	82 / 339	0.023
Transcriptional Regulation by TP53	7 / 484	0.031	4.34e-07	6.29e-05	167 / 259	0.018
Mismatch repair (MMR) directed by MSH2:MSH6 (MutSalpha)	3 / 22	0.001	1.93e-06	1.59e-04	9 / 10	6.79e-04
Mismatch Repair	3 / 23	0.001	2.20e-06	1.59e-04	13 / 17	0.001
Regulation of TP53 Expression	2 / 4	2.59e-04	9.08e-06	4.63e-04	5 / 5	3.40e-04
TP53 Regulates Metabolic Genes	4 / 126	0.008	9.64e-06	4.63e-04	16 / 34	0.002
Diseases of Mismatch Repair (MMR)	2 / 5	3.23e-04	1.42e-05	5.81e-04	4 / 6	4.08e-04
Diseases of DNA repair	3 / 54	0.003	2.79e-05	0.001	11 / 34	0.002
PTEN Regulation	4 / 171	0.011	3.17e-05	0.001	42 / 56	0.004
Regulation of PTEN gene transcription	3 / 70	0.005	6.01e-05	0.002	13 / 15	0.001
TP53 Regulates Transcription of DNA Repair Genes	3 / 86	0.006	1.10e-04	0.003	12 / 17	0.001
Generic Transcription Pathway	8 / 1,586	0.103	1.26e-04	0.003	177 / 884	0.06
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	2 / 17	0.001	1.63e-04	0.004	1 / 2	1.36e-04
RNA Polymerase II Transcription	8 / 1,728	0.112	2.32e-04	0.005	177 / 945	0.064
Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	2 / 22	0.001	2.71e-04	0.005	5 / 9	6.11e-04
PIP3 activates AKT signaling	4 / 322	0.021	3.60e-04	0.006	43 / 88	0.006
Regulation of PTEN mRNA translation	2 / 29	0.002	4.69e-04	0.008	13 / 24	0.002
Gene expression (Transcription)	8 / 1,917	0.124	4.78e-04	0.008	177 / 1,090	0.074
Recognition of DNA damage by PCNA-containing replication complex	2 / 30	0.002	5.02e-04	0.008	3 / 6	4.08e-04
Intracellular signaling by second messengers	4 / 369	0.024	6.01e-04	0.008	43 / 116	0.008
DNA Double-Strand Break Repair	3 / 169	0.011	7.91e-04	0.01	17 / 113	0.008
Diseases of mitotic cell cycle	2 / 38	0.002	8.01e-04	0.01	5 / 5	3.40e-04
Cell Cycle	5 / 733	0.047	9.16e-04	0.011	51 / 451	0.031
Dual Incision in GG-NER	2 / 41	0.003	9.31e-04	0.011	3 / 3	2.04e-04
Oncogene Induced Senescence	2 / 42	0.003	9.76e-04	0.011	4 / 19	0.001

Figure 3. Reactome analysis (https://www.reactome.org/). The panel shows the 25 most relevant pathways sorted by *P* value. These pathways appear predominantly linked to DNA repair processes.

Author Contributions

MF and FZ were involved in clinical care of the patient, performed the excision of the lesion, collected and summarized clinical data, and obtained written consent to publication. RC, MR, and AC performed the morphological analysis of the lesion. BC performed the molecular analysis. BC, EG, and VL evaluated the results of the molecular analysis. MF and AC conceived the idea and drafted the manuscript. All the authors approved the submitted version of the manuscript.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

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Ethical Approval

All the clinic-pathologic investigations detailed in the article have been conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent

Written informed consent for publication of data and images was obtained from the patient.

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