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LETTER TO THE EDITOR

Identification of a novel RAB3IP-HMGA2 fusion transcript in an adult head and neck rhabdomyosarcoma

Dear Editor,

In the landscape of soft tissue sarcoma (STS), adult rhabdomyosarcoma (RMS) represents a very uncommon entity with an incidence of less than 3% (Amer et al., 2019). For these reasons, limited information is currently available about the biological features, molecular profile, and chemotherapy response of this adult disease.

Adult RMS could arise in different body sites with a predilection for extremities, while head and neck region is very rarely reported (WHO Classification of Tumours Editorial Board, 2020). WHO classified RMS into embryonal (ERMS), alveolar (ARMS), pleomorphic (PRMS), and spindle cell/sclerosing variants on the base of morphological and molecular features. In this regard, spindle cell/sclerosing RMS could be divided into three groups showing *MYOD1* mutations, *VGLL2*, and *NCOA2*-associated gene fusions and not recurrent alterations, respectively (Gorunova et al., 2020).

Taking into consideration its relatively recent recognition as a separate RMS entity, the molecular and cytogenetics features of spindle cell/sclerosing subtype have not been elucidated. Thus, in order to provide new insight into the biology of this less understood disease, we investigated the molecular profile of an adult head and neck RMS.

A 74-year-old male patient with a diagnosis of high-grade sclerosing RMS of masseterine parotid with positive surgical margins (bone), Ki-67 positivity 60%, and one lymph node site of micrometastasis was included in the study. Immunohistochemical investigations revealed positivity of tumor cells for vimentin, MyoD1 (Pomella et al., 2021), focal positivity for desmin, myoglobin, myogenin, CD34, and AE1-AE3 cytokeratin (Figure 1a), negativity for S100, STAT6, and P63. Moreover, a widespread nuclear positivity for MDM2 was detected as previously documented (Kikuchi et al., 2013). Next-generation sequencing analysis using a RNA-seq 1385 gene panel detected *RAB3IP-HMGA2* in frame gene rearrangement (Figure 1b,c). The fusion was called by tree different bioinformatics tools and confirmed by sanger sequencing analysis (Figure 1c,d) (Racanelli et al., 2020). Moreover, a *FGFR4* mutation (V550L) already reported was observed (Agaram et al., 2019).

In this scenario, *RAB3IP* has been found associated with tumor cells' proliferation and EMT (Guo et al., 2018). Moreover, *HMGA2* has been show overexpressed in a variety of cancers and its presence is associated with increased metastases rates and poor prognosis (Zhang et al., 2021). Thus, this new fusion transcript could represent a key oncogenic driver for this lesion and could have affected the aggressive behavior and chemoresistance profile of the investigated lesion (Figure 1e–g). This is in line with the observed clinical outcome of the patient who showed several pulmonary and liver metastases and progressed after 4 cycles of doxorubicin. Then received a second line treatment with gemcitabine 3 cycles and after a clinical evidence of progressive disease died.

Interestingly, *HMGA2* and *FGFR4* are located in the same region, which encodes for the *MDM2* amplification detected in this case. Furthermore, the identification of the *FGFR4* druggable mutations provides the rationale for testing new therapeutic options for this disease (McKinnon et al., 2018).

To the best of our knowledge, this is the first case in the literature reporting an adult head and neck sclerosing RMS harboring a *RAB3IP-HMGA2* gene rearrangement. These data could open the door to a diagnosis and prognosis refining together with new therapeutic options for RMS patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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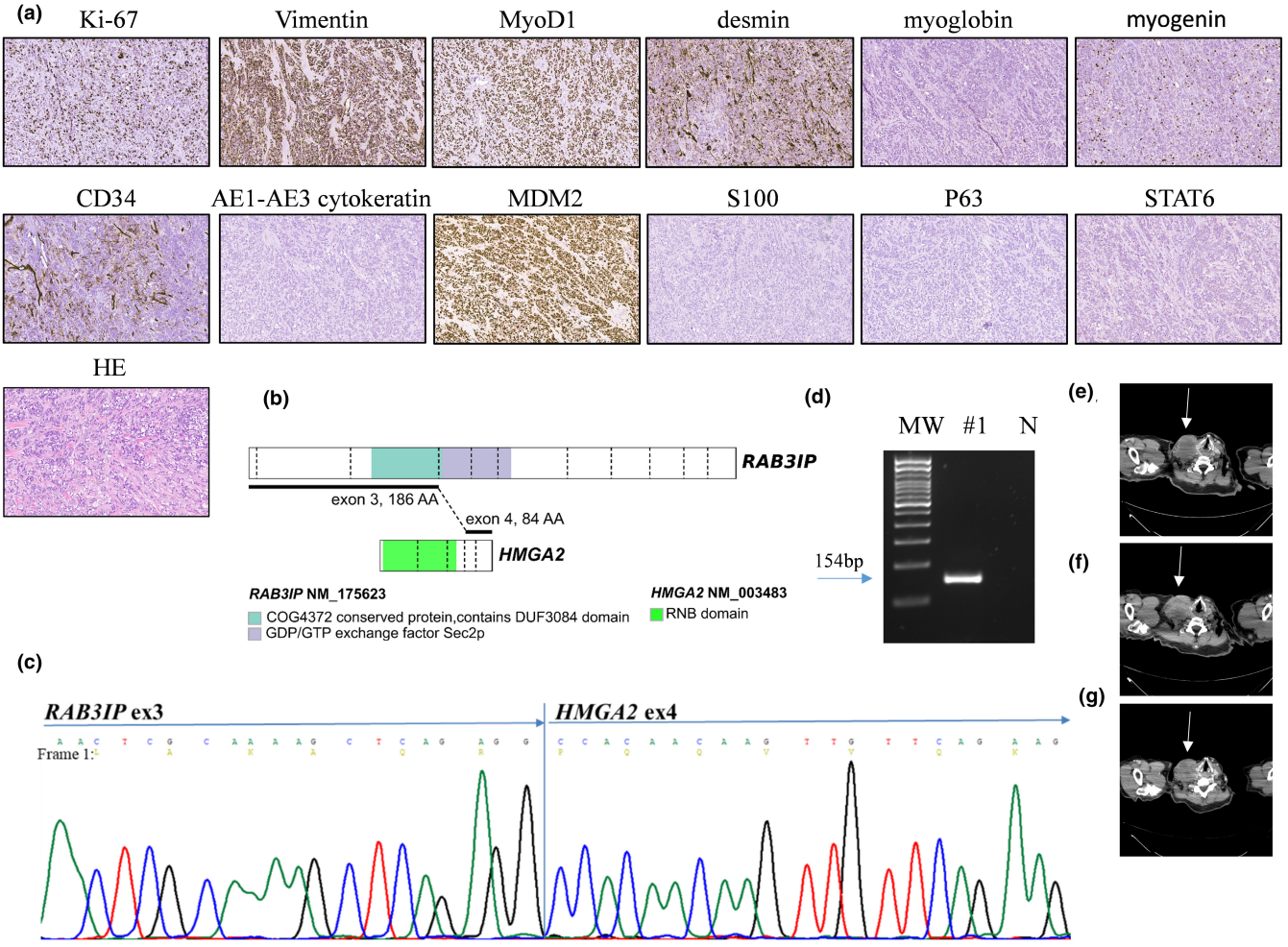

FIGURE 1 (a) Immunohistochemistry (IHC) and hematoxylin and eosin staining of the patient surgical specimen, 10× magnification. (b) RAB3IP and HMGA2 protein diagrams, domain annotations and fusion scheme between RAB3IP exon 3 and HMGA2 exon 4 (RAB3IP, NM_175623, chr12: 70150442, +; HMGA2, NM_003483, chr12: 66345162, +; Human hg19). (c) RAB3IP exon 1- HMGA2 exon 4 fusion Sanger sequencing chromatogram. (d) Agarose gel electrophoresis of Rhabdomyosarcoma sample (#1). Lane MW: DNA Marker (100 bp ladder). Samples 1: RAB3IP-HMGA2 PCR amplified product (154 bp). *N* = Negative. (e) Axial CT scan of right laterocervical before doxorubicin therapy. (f) Axial CT scan of right laterocervical showing progression disease after 4 cycles of doxorubicin. (g) Axial CT scan of right laterocervical after 3 cycles of gemcitabine

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PEER REVIEW

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