*Genes, Chromosomes and Cancer*

WILEY

LETTER TO THE EDITOR

# *NR1D1*::*MAML3* Fusion in an Aggressive Mesenchymal Neoplasm

Minh Chau Ta[1] | Camille Gandon[1] | Maxence Mancini[2] | Philippe Lantier[3] | Olaf Mercier[4] | Samia Mourah[2,5] | Maxime Battistella[1,5]

[1]Service de Pathologie, Hôpital Saint-Louis, Paris, France | [2]Service de Génomique Des Tumeurs et Pharmacologie, Hôpital Saint-Louis, APHP, Paris, France | [3]Service de Pathologie, Hôpital Marie Lannelongue, Le Plessis-Robinson, France | [4]Service de Chirurgie Thoracique et Vasculaire, Hôpital Marie Lannelongue, Le Plessis-Robinson, France | [5]Université Paris Cité, INSERM U1342, Paris, France

**Correspondence:** Minh Chau Ta (minhchau.ta@aphp.fr)

**Received:** 13 February 2025 | **Revised:** 1 April 2025 | **Accepted:** 3 April 2025

**Keywords:** EMA | epithelioid | Erg | mesenchymal tumor | sternal cyst | undifferentiated sarcoma

## ABSTRACT

*NR1D1*-rearranged tumors are distinct mesenchymal neoplasms with epithelioid morphology and aggressive potential. This report presents an 85-year-old male with a slow-growing sternal mass identified as a pseudo-cyst, characterized by a dense proliferation of epithelioid tumor cells. These cells exhibited pale cytoplasm and uniform oval nuclei, with some areas of spindle cells and extensive necrosis. The mitotic count was 12 per 1.7 $mm^2$. Immunohistochemical analysis showed positivity for EMA, ERG, AE1AE3, and CK7, but negativity for SMA, desmin, CD117, CD31, SOX10, MelanA, synaptophysin, INSM1, CK20, CD34, TTF1, WT1, caldesmon, myogenin, and collagen IV. INI1 expression was preserved. The Ki67 index was high. Whole-transcriptome sequencing revealed an in-frame *NR1D1*::*MAML3* fusion, retaining two key protein domains of *NR1D1*. Nine months post-diagnosis, the patient developed pleural, bilateral lung, and bone metastases. This case underscores the necessity of molecular analysis for precise tumor classification, given the tumor's varied morphological features and poor prognosis.

To the Editor,

In light of the significant article by Lacambra et al. describing four cases of *NR1D1*-rearranged tumors [1], we report an additional case of a mesenchymal neoplasm with an *NR1D1*::*MAML3* fusion, contributing to the growing spectrum of *NR1D1*-related tumors. An 85-year-old male presented with a gradually enlarging sternal mass over several months without skin changes or systemic symptoms. Radiologic evaluation revealed a 5.5 cm cystic structure in the subcutis of the sternum. Surgical resection was performed.

Histologically, the subcutaneous lesion showed an infiltrative growth pattern with a combination of morphologies. The bulk of the tumor formed a pseudo-cyst with a wall consisting of a dense proliferation of predominantly epithelioid tumor cells (Figure 1A,B). These cells had pale, poorly defined cytoplasm and oval, uniform nuclei with vesicular chromatin (Figure 1C). Some areas of spindle cells were observed (Figure 1D). Mitotic count was 12 mitoses per 1.7 $mm^2$. The stroma was collagenous, lacking a myxoid component. The proliferation infiltrated peripheral adipose tissue, while

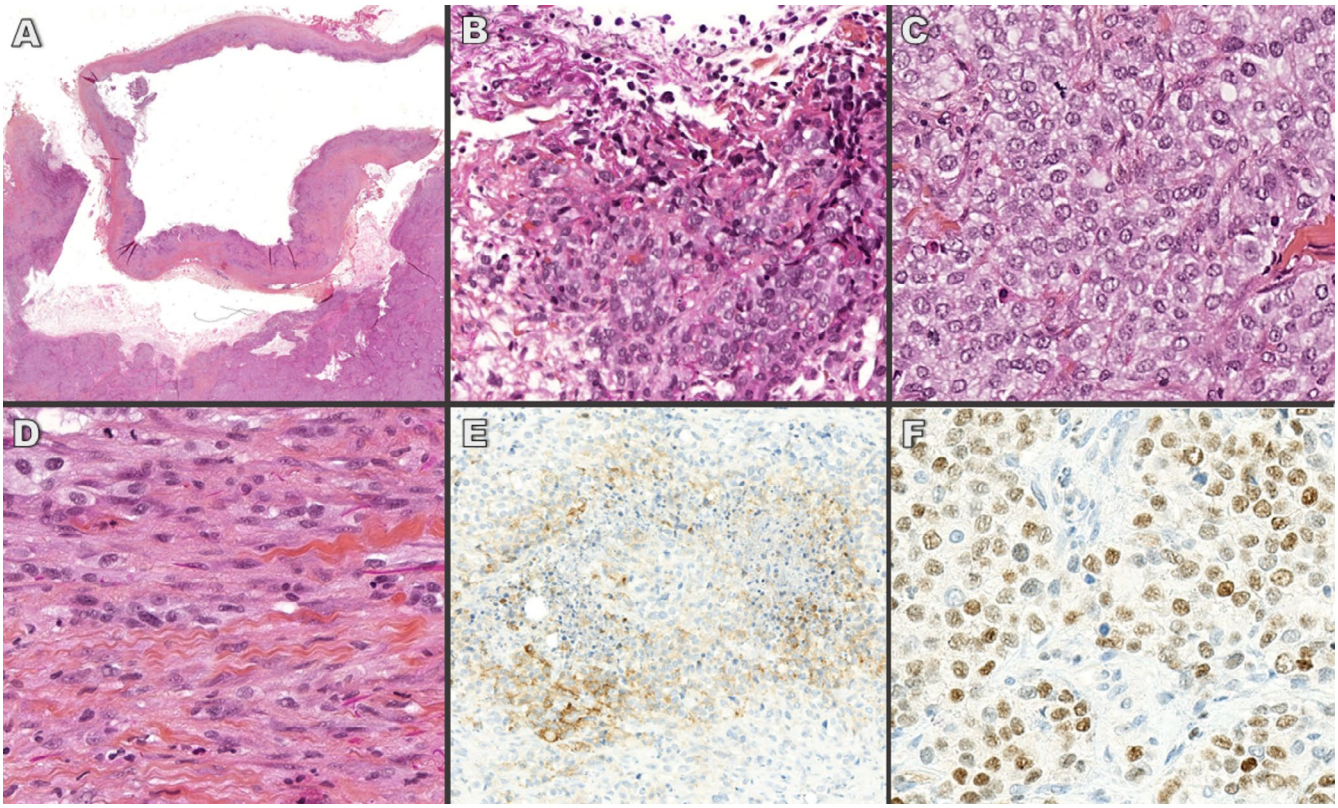


**FIGURE 1** | Histopathologic features of a neoplasm with an *NR1D1::MAML3* fusion. Pseudo-cyst with a wall consisting of a dense proliferation of predominantly epithelioid tumor cells (A, H&E, 50× and B, H&E, 300×). Large pale epithelioid cells with oval uniform nuclei and vesicular chromatin (C, H&E, 400×). Spindle cells were observed in some areas, surrounded by a collagenous stroma (D, H&E, 400x). Positive staining for EMA (E, IHC, 300×) and ERG (F, IHC, 400×).

extensive necrosis bordered the cavity, representing less than half of the tumor.

Immunohistochemically, the tumor cells were positive for EMA and ERG (Figure 1E,F), focally positive for AE1AE3, CK7, and membranous Beta-catenin. They were negative for SMA, desmin, CD117, CD31, SOX10, MelanA, synaptophysin, INSM1, CK20, CD34, TTF1, WT1, caldesmon, myogenin, and collagen IV. INI1 expression was preserved. The Ki67 index was high.

Whole-transcriptome sequencing analysis (RNAseq SureSelect XT HS2 RNA System, Agilent) identified an in-frame *NR1D1*(exon 6)::*MAML3*(exon 2) gene rearrangement (Figure 2). Additional fusions of uncertain significance were detected, including *SNORA57*::*HSPA5* and *GLIS3*::*KSR1*, along with other low-frequency fusion events (Figure 2). The *NR1D1*::*MAML3* fusion retained the zinc finger and ligand-binding domains of *NR1D1* (Figure 2).

Based on the "composite" morphology, immunohistochemical profile, and molecular findings, the diagnosis of an *NR1D1*-rearranged mesenchymal neoplasm was made. The patient developed pleural, bilateral lung, and bone metastases 9 months after the initial diagnosis.

Our case expands the clinicopathologic spectrum of *NR1D1*-rearranged tumors [1–5]. In line with the observation that tumors associated with *NR1D1* fusions frequently resemble other neoplasms, our case exhibited significant epithelioid characteristics and focal keratin expression, making it challenging to distinguish from epithelial tumors. The pseudo-cystic structure, extensive necrosis, large pale epithelioid cells, spindle cell areas, and high Ki67 index aligned with previous reports [1–5]. Notably, this case showed ERG expression, representing the second case of an *NR1D1*-rearranged neoplasm with ERG positivity [4].

To conclude, this case of an *NR1D1*::*MAML3*-rearranged mesenchymal neoplasm highlights the misleading morphological features and the aggressive nature associated with *NR1D1*-rearranged tumors. It emphasizes the necessity for molecular analysis to ensure precise tumor classification, given the tumor's varied morphological features and poor prognosis.

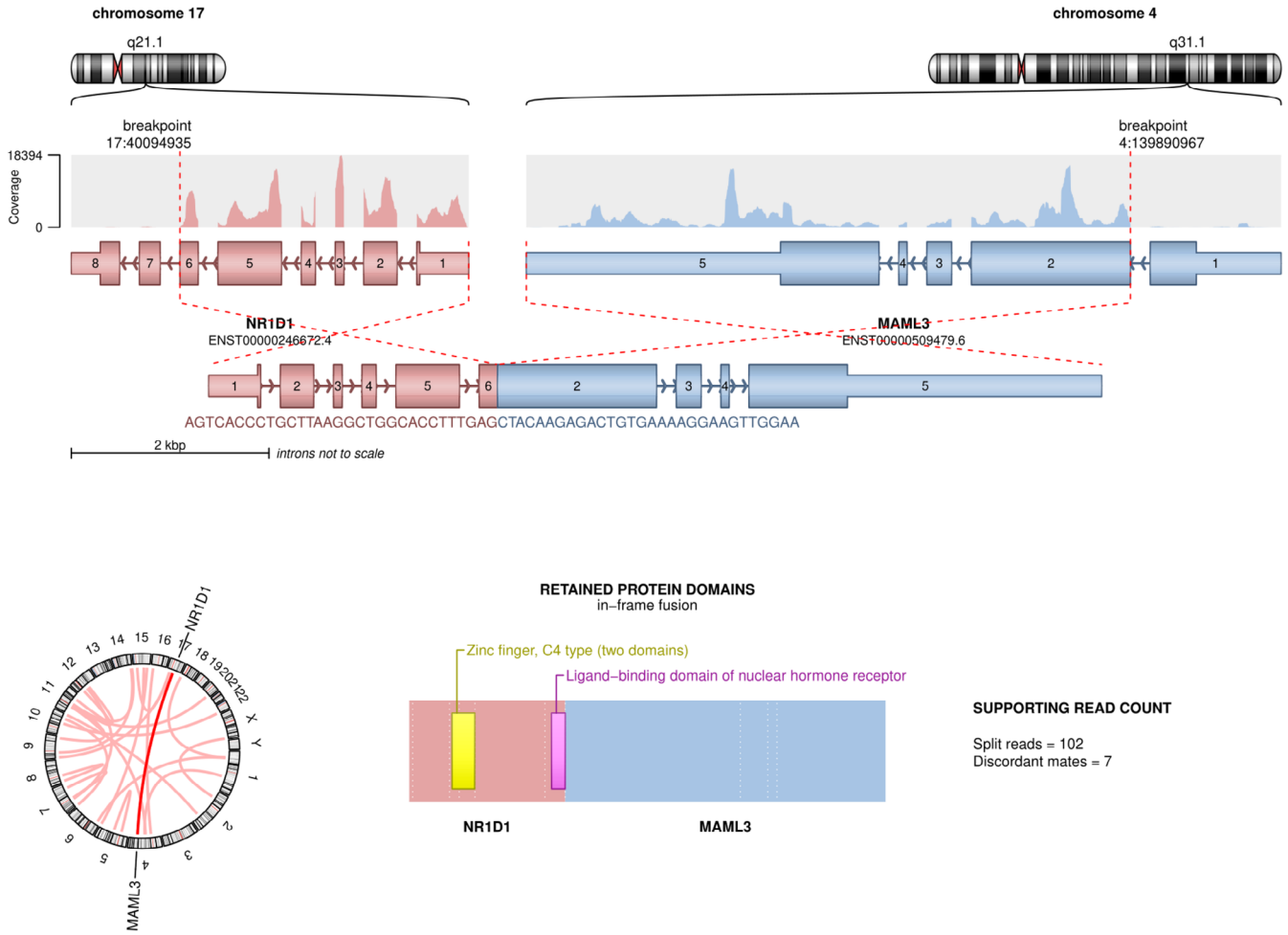


**FIGURE 2** | Molecular findings in the tumor. *NR1D1* (ENST00000246672.4) exon 6 is fused in-frame to *MAML3* (ENST00000509479.6) exon 2. The Circos plot illustrates the *NR1D1*::*MAML3* fusion, alongside additional fusion events of uncertain significance (*SNORA57*::*HSPA5* and *GLIS3*::*KSR1*), as well as other low-frequency fusion events (fusion fragments per million total reads [FFPM] < 0.1). The *NR1D1*::*MAML3* fusion retains two conserved protein domains of *NR1D1*: The Zinc finger domain and the Ligand-binding domain of nuclear hormone receptor.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Minh Chau Ta
Camille Gandon
Maxence Mancini
Philippe Lantier
Olaf Mercier
Samia Mourah
Maxime Battistella

## References

1. M. D. Lacambra, C. R. Antonescu, C. Chow, et al., "Expanding the Spectrum of Mesenchymal Neoplasms With *NR1D1*-Rearrangement," *Genes, Chromosomes & Cancer* 61 (2022): 420–426.

2. M. Komatsu, N. Yamamoto, T. Kawamoto, et al., "Soft Tissue Tumor With Novel *NR1D1-MAML1* Fusion in a Pediatric Case," *Virchows Archiv* 477 (2020): 891–895.

3. H. Nakamura, Y. Kukita, S. Takenaka, and T. Yagi, "Malignant Epithelioid Soft Tissue Tumour With the *NRID1-MAML1* Fusion," *Histopathology* 79, no. 6 (2021): 1112–1114.

4. L. M. Warmke, C. D. Collier, and J. L. Davis, "NR1D1::MAML1 Epithelioid and Spindle Cell Sarcoma Mimicking Pseudomyogenic Hemangioendothelioma in Core Biopsy: A Case Report and Review of the Literature," *Genes, Chromosomes & Cancer* 62, no. 11 (2023): 655–662.

5. T. Yin, P. Zhu, I. W. Lao, et al., "*NR1D1*-Rearranged Soft Tissue Tumour: A Clinicopathological and Molecular Analysis of Four Additional Cases," *Histopathology* 84, no. 4 (2024): 661–670.