Sarcoma with MXD4-NUTM1 gene fusion

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Introduction

NUTM1-rearranged neoplasia is an emerging group of tumours which share the underlying NUTM1 gene rearrangements. In a retrospective study, 26 NUTM1-rearranged neoplasms were reported with two novel gene markers described: MAX gene associated protein (MGA) and MAX dimerization protein 4 (MDX4). We herein describe a case of sarcoma with MXD4-NUMT1 gene fusion occurring in the small bowel mesentery.

Case Report

The patient, Ms. Chang, was a 53 years old lady who presented with intussusception in 4/2006 with small bowel resection done. Examination of the small bowel revealed a 2 cm small bowel tumour. Pathology showed low grade gastrointestinal stromal tumour. Follow-up PET-CT in 5/2020 showed a 9.3 cm intra-peritoneal mass in the central lower abdomen above the uterus. The mass was removed with part of the small intestine in 7/2020.

Pathology

Macroscopic appearance

There was a tumour in the mesentery of the small bowel measuring 13 x 11.5 x 7 cm. It had a pushing border with white firm cut surface. There was no involvement of the small bowel wall.

Microscopic appearance

Sections show tumour in the mesentery without bowel wall involvement. The tumour is composed of infiltrative, non-cohesive round cells with mildly irregular nuclei, fine chromatin, distinct nucleoli and moderate amount of densely eosinophilic cytoplasm. Necrosis is noted. Mitosis is occasionally seen.

Immunohistochemistry

The tumour cells showed diffuse staining for NUT. There is perinuclear dot-like staining for epithelial markers (cam5.2, MNF116 and AE1/3) and desmin. There is membranous staining for CD99. The tumour cells are negative for lymphoid markers (LCA, CD20, CD3, CD79a, CD20, CD30, Kappa and lambda, OCT2, BOB1, CD138, CD163 and MPO), neuroendocrine markers (synaptophysin and chromogranin), CKIT, DOG1, actin, myoD1, calretinin, melanocytic markers (S100, HMB45 and melan A), CD34 and SALL4. The INI-1 and BRG1 staining are intact. The ETV4 and BCOR staining are negative.

Molecular studies

Illumina pan-cancer RNA-sequencing panel analysis performed at the Prince of Wales Hospital showed MXD4-NUTM1 chimeric fusion transcript.

Discussion

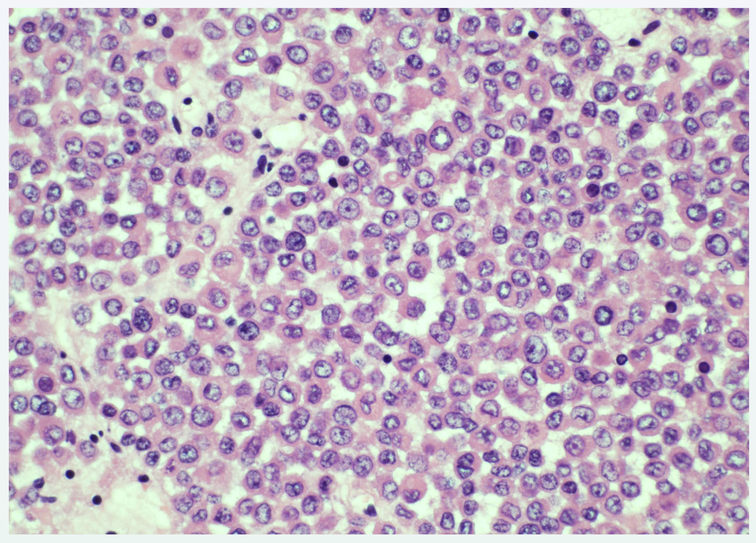
There is expanding histological appearances and clinical characteristics to tumours with NUTM1 rearrangements. Apart from the NUT midline carcinoma occurring in midline structures of young adults showing epithelial differentiation and abrupt keratinization, there are NUTM1 rearranged tumours with sarcomatoid or small round cell morphologies. Middle aged adults and elderlies are also affected. Non-midline locations, such as viscera, soft tissue, and as in this case, small bowel mesentery, are involved. Apart from the commonest fusion markers bromodomain-containing 4 (BRD4) and bromodomain-containing 3 (BRD3), novel fusion partners are identified: MGA and MDX4. They are both members of the MAX-interacting transcription factor network. Both fusion partner genes are associated with tumours with sarcomatoid appearance and the lack of epithelial differentiation (CK negative); spindled cells in myxoid stroma with resemblance to extra-skeletal myxoid chondrosarcoma, and small round cell features. These non-BRD genes may explain the difference in response to extraterminal domain inhibitor therapy. Therefore, the identification of NUTM1 fusion partners by FISH or next generation sequencing may become an essential component for appropriate clinical management. Immunostaining for NUTM1 are positive amongst NUTM1 rearranged tumours, including those with novel fusion partners MDX4 and MGA. Hence, NUT immuostain may serve as an effective screening test for NUTM1 rearrangement tumours, and should be included in the immunohistochemical panel in working up small round cell tumours.

Conclusion

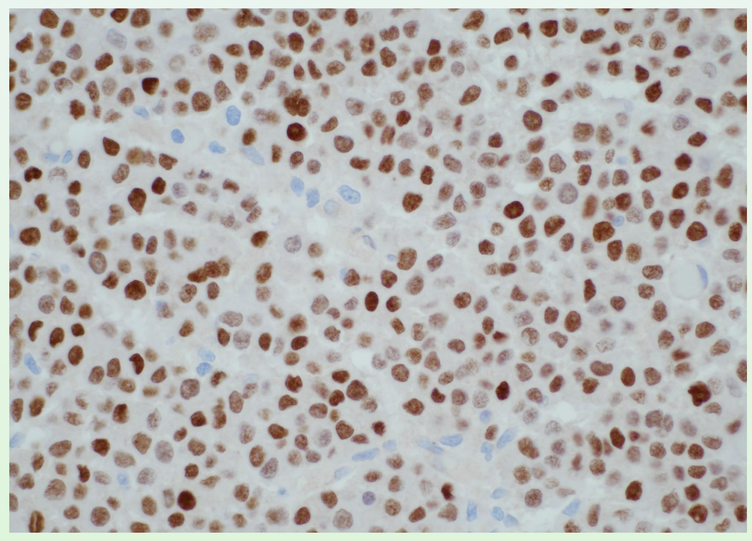
The findings of this case report further illustrates the presence of tumours with NUTM1 gene rearrangements that occur outside the classic clinicopathological setting of NUT carcinoma, and highlights the importance of immunohistochemical staining and molecular testing to identify this emerging group of tumours. However, due to the rarity of these tumours, the clinical and prognostic significance of different gene partners remains unknown, and its relationship with the traditional NUT midline carcinoma remains unclear. Further studies are required for elucidation.

Reference

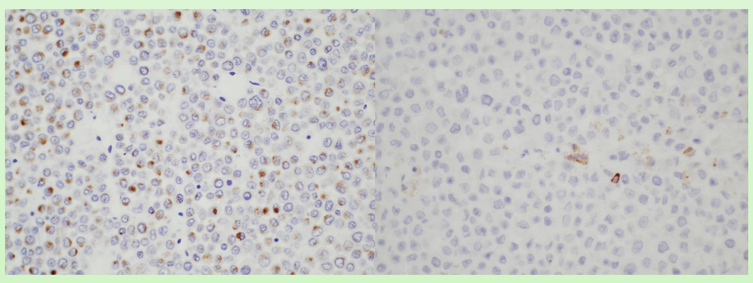
1. Todd M. Stevens, et al. NUTM1-rearranged neoplasia: a multi-institution experience yields novel fusion partners and expands the histologic spectrum.” Modern Pathology (2019) 32:764-773
2. Dickson BC, Sung YS, Rosenblum MK, et al. NUTM1 Gene Fusions Characterize a Subset of Undifferentiated Soft Tissue and Visceral Tumors. *Am J Surg Pathol*. 2018;42(5):636-645. doi:10.1097/PAS.0000000000001021
3. Tamura R, Nakaoka H, Yoshihara K, et al. Novel MXD4-NUTM1 fusion transcript identified in primary ovarian undifferentiated small round cell sarcoma. *Genes Chromosomes Cancer*. 2018;57(11):557-563. doi:10.1002/gcc.22668
4. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Lüer SC, Muhammed S, Evans AG, Sholl LM, Rosai J, Giraldi E, Oakley RP, Rodriguez-Galindo C, London WB, Sallan SE, Bradner JE, French CA. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res. 2012 Oct 15;18(20):5773-9. doi: 10.1158/1078-0432.CCR-12-1153. Epub 2012 Aug 15. PMID: 22896655; PMCID: PMC3473162.
5. Stathis A, Zucca E, Bekradda M, Gomez-Roca C, Delord JP, de La Motte Rouge T, Uro-Coste E, de Braud F, Pelosi G, French CA. Clinical Response of Carcinomas Harboring the BRD4-NUT Oncoprotein to the Targeted Bromodomain Inhibitor OTX015/MK-8628. Cancer Discov. 2016 May;6(5):492-500. doi: 10.1158/2159-8290.CD-15-1335. Epub 2016 Mar 14. PMID: 26976114; PMCID: PMC4854801.



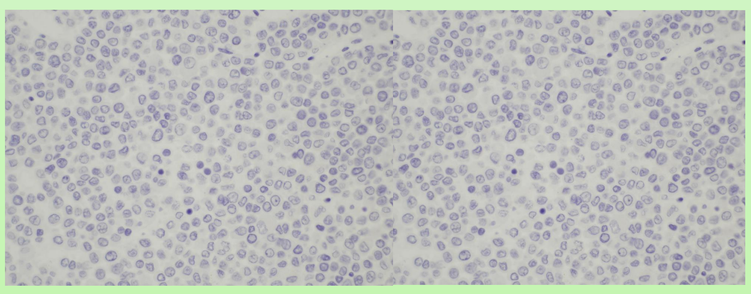
H&E



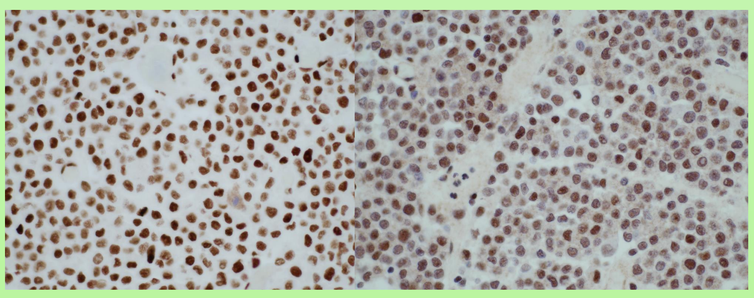
NUT



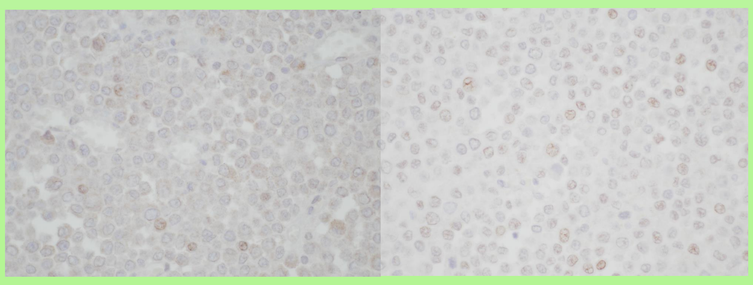
AE1/3 LCA



C-kit DOG1



BRG1 INI-1



ETV6 BCOR