Lesson of the Month

**FUS::CREM-rearranged malignant epithelioid neoplasm mimicking neuroendocrine neoplasm of unknown primary**

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**Case summary**

A 76-year-old woman presented with abdominal pain. Diagnostic investigations suggested peritoneal carcinomatosis. Histological examination of laparoscopic biopsies showed large epithelioid cells forming sheets intermingled with some lymphocytes. There was no clearly distinguishable stroma. Immunohistochemistry showed diffuse and strong expression of cytokeratin AE1/AE3, synaptophysin and chromogranin-A (Figure 1A). There was some weak and/or focal expression of Wilms’ tumour protein 1 (WT-1), keratin 5/6, mucin 4 (MUC4) and S-100 protein, whereas stainings for keratin 7, keratin 20, calretinin, D2-40, hepatocyte paraffin 1 (HepPar-1), arginase-1, Melan-A, GATA binding protein 3 (GATA-3), paired box gene 8 (PAX-8), anaplastic lymphoma kinase (ALK) and CD56 remained negative. Mitoses were not observed. Ki-67 proliferation index was 3.5%. Histological examination of material obtained after cytoreductive surgery again showed a well-vascularised tumour composed of nodules of large epithelioid cells with eosinophilic or clear cytoplasm accompanied by peripheral lymphocytic infiltrates (Figure 1B–D), and a diagnosis of metastatic infiltration by a neuroendocrine neoplasm of unknown primary was proposed. This tentative diagnosis was further supported by elevated serum chromogranin and neurone-specific enolase levels.

Postoperative follow-up examinations demonstrated local and distant recurrence with lung, pleural, bone, liver and subcutaneous metastases. Targeted DNA and RNA next-generation sequencing (NGS) was performed. No point mutations were detected but a FUS::CREM fusion was identified using FoundationOne CDx panel. Hence, a diagnosis of FUS::CREM-rearranged malignant epithelioid neoplasm was retained. This fusion was confirmed by fluorescence in-situ hybridisation (FISH) using the Vysis LSI FUS break-apart FISH probe kit, following the manufacturer’s recommendations and a validated protocol for routine diagnosis (Figure 2).

**Comments**

Although neuroendocrine neoplasms are defined by the expression of synaptophysin and chromogranin-
A. these markers may also be expressed in other tumours such as adrenocortical carcinomas, adeno-carcinomas and sarcomas. With increasing use of targeted RNA NGS in daily pathology practice, several new molecularly defined entities are emerging. CREM-rearranged neoplasms are rare tumours representing the CREB fusion family. They include subsets of clear cell sarcomas, clear cell carcinomas of the head and neck region and angiomatoid fibrous histiocytomas. EWSR1/FUS::CREM fusions were recently recognised in a group of unclassified epithelioid mesenchymal neoplasms essentially occurring in mesothelial-lined cavities (mainly the abdomen) and not corresponding to any known EWSR/CREB-rearranged entity. These tumours are definitely malignant with a propensity for peritoneal and distant recurrence, as in our case. They typically display monotonous epithelioid morphology with variable cytoplasmic clearing, some intratumoral or peripheral lymphocytes and sparse stroma. Most cases express keratin and epithelial membrane antigen (EMA). At least focal synaptophysin expression has been reported in several cases whereas, including our case, chromogranin expression has been observed in only two cases. However, it must be mentioned that in the initial series describing FUS::CREM fusions in tumours of mesothelial-lined cavities, neuroendocrine marker expression was not tested.5

We share our case to draw attention to the misleading histological and immunophenotypical characteristics of this group of rare tumours. Our case further underlines the immunophenotypical heterogeneity of EWSR1/FUS::CREM fusion-driven mesenchymal neoplasms that may be mistaken for epithelial and/or neuroendocrine metastatic tumours of unknown primary. In both chromogranin-expressing EWSR1/FUS::CREM rearranged tumours described so far, FUS was the CREM fusion partner. Although EWSR1/FUS::CREM-rearranged malignant epithelioid neoplasms are extremely rare mimickers of metastatic neuroendocrine neoplasms, this entity should be considered in the differential diagnosis in case of unusual clinical and/or histopathological presentation.

As it is not clear, at present, if the reported intra-abdominal epithelioid tumours harbouring EWSR1/FUS::CREM fusions truly represent a single stand-alone entity we cannot, however, exclude that the present case represents a true neuroendocrine neoplasm with this fusion. Larger series will be needed to understand the clinical significance of neuroendocrine differentiation in neoplasms characterised by such fusions.

Conflicts of interest
The authors declare no conflicts of interest.

References

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