Histopathology

Histopathology 2021 DOI: 10.1111/his.14579

Lesson of the Month

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

DOI: 10.1111/his.14579

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-

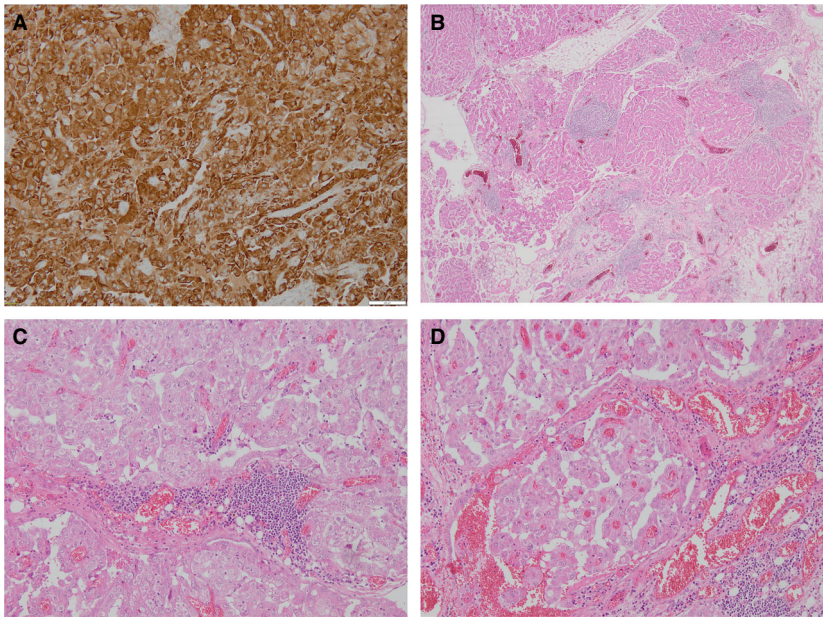

Figure 1. Histological examination revealed a well-vascularised tumour composed of large epithelioid cells expressing chromogranin-A (**A**). The neoplastic cells formed nodules accompanied by lymphocytic infiltrates (**B–D**).

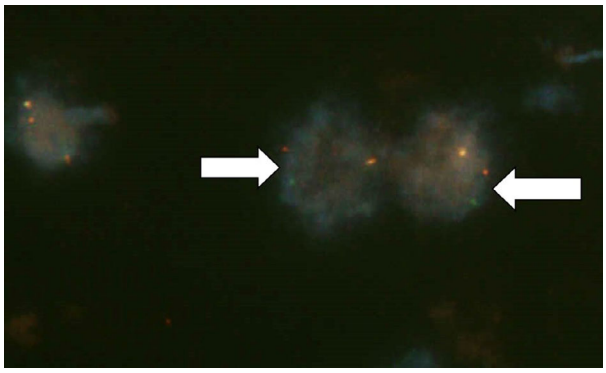

Figure 2. *FUS* gene fusion was confirmed by fluorescence *in-situ* hybridisation (FISH) using the Vysis LSI FUS break-apart FISH probe kit. Clear dissociations of red and green spots were observed for 22% of the cells analysed (white arrows), highlighting the rearrangement of the gene.

A, these markers may also be expressed in other tumours such as adrenocortical carcinomas, adenocarcinomas and sarcomas.[1] 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.[2] *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.[2–5] 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).[2,4,5] At least focal synaptophysin expression has been reported in several cases[2,4,6] whereas, including our case, chromogranin expression has been observed in only two cases.[4] However, it must be mentioned that in the initial series describing *FUS::CREM* fusions in tumours of mesothelium-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[6] 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.

Pieter Demetter[1]
Ahmad Awada[2]
Philippe Aftimos[2]
Gabriel Liberale[3]
Christiane Jungels[2]
Maria Gomez-Galdon[1]
Manuel Saiselet[1]
Nicolas de Saint Aubain[1]
[1]*Department of Pathology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels,* [2]*Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, and* [3]*Department of Surgical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

References

1. Kasajima A, Konukiewitz B, Schlitter AM *et al.* Mesenchymal/non-epithelial mimickers of neuroendocrine neoplasms with a focus on fusion gene-associated and SWI/SNF-deficient tumors. *Virchows Arch.* 2021. https://doi.org/10.1007/s00428-021-03156-9
2. Yoshida A, Wakai S, Ryo E *et al.* Expanding the phenotypic spectrum of mesenchymal tumors harboring the EWSR1–CREM fusion. *Am. J. Surg. Pathol.* 2019; **43**; 1622–1630.
3. Thway K, Fischer C. Mesenchymal tumors with EWSR1 gene rearrangements. *Surg. Pathol. Clin.* 2019; **12**; 165–190.

4. Agaimy A, Stoehr R, Otto M *et al*. Intra-abdominal *EWSR1/FUS–CREM*-rearranged malignant epithelioid neoplasms: two cases of an emerging aggressive entity with emphasis on misleading immunophenotype. *Virchows Arch.* 2021. https://doi.org/10.1007/s00428-021-03140-3
5. Argani P, Harvey I, Nielsen GP *et al*. EWSR1/FUS–CREB fusions define a distinctive malignant epithelioid neoplasm with predilection for mesothelial-lined cavities. *Mod. Pathol.* 2020; **33**; 2233–2243.
6. Shibayama T, Shimoi T, Mori T *et al*. Cytokeratin-positive malignant tumor in the abdomen with *EWSR1/FUS–CREB* fusion: a clinicopathologic study of 8 cases. *Am. J. Surg. Pathol.* 2021. https://doi.org/10.1097/PAS.0000000000001742