

FAMILIAL CANCER CLINICAL UNIT

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OVERVIEW

Lynch syndrome is a very complex entity associated with high risks for a wide variety of malignancies, including colorectal, endometrial, ovarian, gastric, urinary tract, pancreatic, biliary, small intestinal, prostatic, and brain cancers. Until now, the malignancies developed in people with Lynch syndrome were treated exactly in the same way as their sporadic counterparts. However, recent therapeutic advances in the immunologic effects of microsatellite instability (MSI), the hallmark of Lynch syndrome associated tumours, have resulted in important changes in the treatment of these patients.

MSI, by definition, is characterised by the somatic accumulation of mutations, which subsequently produce potentially antigenic frameshift neopeptides that account for the infiltrating lymphocyte reaction classically observed

in Lynch-associated tumours. The recent emergence of immune checkpoint inhibitors that work on the patients' own immune system has led to the use of this underlying biological characteristic to advance in the treatment of Lynch syndrome-associated tumours.

The Familial Cancer Clinical Unit (FCCU) is not only committed to screening blood samples with the aim of identifying germline mutations, but also to analysing tumour samples to determine their microsatellite status. Both findings play a critical role in the understanding of the molecular drivers of malignancy and the implementation of innovative precision-based therapies.

CLINICAL, DIAGNOSTIC AND RESEARCH HIGHLIGHTS

The clinical and diagnostic activities carried out by the FCCU through the consultancy in the Medical Oncology Department of Fuenlabrada's University Hospital, have contributed to the selection of patients who are good candidates for targeted therapies. In order to extend the study, we apply a multigene panel test to an increasingly larger number of pathologies. Ovarian cancer (OC) for instance, is a genetically heterogeneous malignancy that is potentially driven by multiple aberrant molecular pathways. Germline *BRCA1/2* mutations account for 65–85% of all hereditary OC, while mutations in Lynch genes (DNA mismatch repair genes) are responsible for 10–15% of these hereditary OC. Germline mutations drive the therapeutic strategy: OC associated to *BRCA1/2* mutations have a demonstrated sensitivity to PARP inhibitors, while immune checkpoint inhibitors are indicated for metastatic solid tumours associated with DNA mismatch repair deficiency.

Our clinical and diagnostic activities this year can be summarised as follows: 550 patients visited our consultancy at HUF (8.69% increase over 2017); and 508 genetic diagnostic studies were performed in the FCCU laboratory (18.69% increase). Among these studies, we identified 25 tumours with MSI, all of them potential candidates to be treated with monoclonal antibodies that target PD-1.

Our research in colorectal cancer (CRC) focuses on early-onset forms and multiple primary tumours. We recently reported the largest series of Synchronous Colorectal Cancers (SCRC), in which clonality was analysed by Single-Nucleotide Polymorphism array, and the subsequent statistical application; we were the first to correlate it with clinical phenotypes. Thirty-six per cent of our SCRC fulfilled clonality features. The existence of clonality within SCRC has important consequences throughout therapeutic management. The stratification in different categories may also serve as a starting point to more selectively analyse the molecular basis of SCRC and its relationship with environmental factors.

The FCCU also focuses its research efforts on less frequent cancer predisposition syndromes. One of these is the PTEN hamartoma tumour syndrome (PHTS), in which several aspects such as the high clinical heterogeneity usually result in a late diagnosis. We have studied this pathology at the clinical and molecular level in the largest series of Spanish patients with PHTS (145 probands). Overall, our findings are consistent with the syndrome descriptions in other populations, with a few exceptions such as a higher proportion of carriers of mutations in *PTEN* exon 1. We have also discussed the usefulness of the different diagnostic criteria proposed to date for this disease and have suggested recommendations based on our results. We are currently focusing on the search for phenotype modifiers, as in the case of the *KLLN* gene, as well as for other genetic factors that may explain the disease in *PTEN* wild type patients. For this last purpose, we are using a gene panel to look for mutations on the main pathway antagonised by PTEN – the PI3K/AKT/mTOR pathway – and are analysing whole exome sequencing data from selected cases. Our study continues to contribute to a better definition of PHTS and to help accelerate the diagnosis of the patients.

Addressing the functional consequence of germline missense variants involved in cancer genes is very important when prophylactic surgical removal of organs is the only therapeutic option to prevent the development of an aggressive cancer. In this context, we found 3 unrelated families with hereditary diffuse gastric cancer carrying the same germline missense variant in the *CDH1* gene: c.1679C>G. Through genetic and *in vitro* studies, we explored the effect of this variant and finally demonstrated its deleterious effect, suggesting that gastrectomy should be considered in patients harbouring this variant. ■

PUBLICATIONS

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