BDIAP/ESP 2020 Fellowship Report

- Name of bursary recipient : Dr Abhishek Dashora
- Year Bursary awarded : 2020
- Trust where employed: Royal Free Hospital NHS Trust
- Trainee grade: ST3 Histopathology
- Topic of research: Analysis of Endometrial Carcinoma with subclonal p53 Expression

The Cancer Genome Atlas (TCGA) has identified 4 prognostically relevant molecular groups of endometrial carcinoma (EC). The group with the worst clinical outcome is characterized by driver mutations in *TP53 (*p53abn*)*. Immunohistochemistry (IHC) for p53 protein has recently been shown to be a reliable surrogate for underlying *TP53* mutation in EC biopsy material. Some cases, however, show a confusing p53 expression pattern that is heterogeneous or subclonal, showing a combination of mutant patterns or of mutant and normal staining in different areas of the same tumour. A recent study of 177 cases with matched p53 IHC and *TP53* mutation status showed a subclonal pattern in 9 cases, 4 of which harboured detectable *TP53* mutations while 5 did not. Furthermore, 5 cases showed either a pathogenic mutation in the exonuclease domain of DNA polymerase epsilon gene (POLEmut) or a mismatch repair defect (MMRd). The clinical relevance of these cases is therefore unknown as these could fall into any of the 4 TCGA EC groups.

This study was a part of a larger ongoing project and Prof Naveena Singh gave me this exciting opportunity to be a part of it. Our aim was to study EC cases showing subclonal p53 expression to determine which TCGA categories these should be assigned to; in addition, to develop practical guidance for the interpretation of this novel and poorly understood expression pattern.

Through multicentric collaboration between Barts Health NHS trust London; Vancouver General Hospital Canada and other affiliate institutions, representative tumour specimens of 278 ECs were available for analysis. They were classified into TCGA/ProMise categories using p53 and MMR IHC on whole sections, together with pathogenic *POLE* mutation testing using targeted next generation sequencing (NGS). Cases with subclonal p53 IHC expression involving ≥5% of tumour underwent directed sampling [a single 1mm core for each differentially staining area] and *TP53* sequencing through NGS.

It has been demonstrated that *TP53* mutation occurring in context of POLEmut and MMRd are secondary passenger mutations that do not carry the same poor prognosis as driver p53 mutations.
Our analysis shows that abnormal subclonal p53 expression is always a result of underlying *TP53* mutation.

We concluded that subclonal p53 IHC staining is relatively uncommon and reflects an underlying pathogenic *TP53* mutation with variable IHC expression. This is most frequently encountered in EC's known to carry a high tumour mutational burden (MMRd, POLEmut); in this context *TP53* mutation is reported to be a secondary event unassociated with adverse prognosis. When seen in MMR proficient and *POLE* wild type cases, this pattern appears to be indicative of p53abn EC.

Histopathology and immunohistochemistry were the basis of case selection in this project and further molecular studies were undertaken to better categorize them. This does emphasize that integration of molecular diagnostics into histopathology is imperative in the current era of personalized medicine. As a histopathology trainee it was an amazing experience to have hands on experience in molecular pathology which supplemented my ongoing training.

Due to COVID-19 pandemic, the ESP/IAP 2020 meeting was a virtual event and the study was presented in the form of e-poster with a pre-recorded commentary. The virtual format of the meeting was excellent in terms of availability of lectures and presentations, however there were reduced opportunities for networking and feedback.

I am very thankful for this fellowship award by BDIAP which made this possible and enhanced my histopathology training and research experience.