

Mismatch repair protein expression defects in endometrioid endometrial adenocarcinoma

Mark R. Brincat, Tiffany Buhagiar, Sharon Falzon, Sabrina Ariff, Simona Bugeja, James Debono, Yves Muscat Baron, Ian Said Huntingford, Neville Calleja

The study entitled 'Mismatch repair protein expression defects in endometrioid endometrial adenocarcinoma' is the first ever study to investigate the prevalence of mismatch repair protein deficiency in Maltese endometrioid endometrial cancer (EEC) cases as well as the correlation of mismatch repair (MMR) protein expression with age at diagnosis. It was undertaken because more and more evidence is emerging on chemotherapeutic resistance in MMR deficient tumours, as well as on the proven efficacy of targeted immune checkpoint blockade drugs for these patients.

200 EEC cases were retrospectively identified and categorised into three arms: 151 cases above age 50 at diagnosis, 49 cases at or below age 50 at diagnosis and 30 controls with benign endometrial tissue sampling. Pathology case slides were re-examined by an independent pathologist to confirm the diagnosis and identify the block best representing the tumour. Four new slides were recut per case and immunohistochemistry performed looking for MLH1, PMS2, MSH2, and MSH6 proteins. Protein expression was analysed semiquantitatively using Allred scoring.

This study found that 31% of the overall EEC cases were deficient for one or more MMR-proteins. Dual loss of the MLH1-PMS2 proteins was the most common deficiency, occurring in 24.5% of cases. Loss of MSH2-MSH6 protein expression represented 3.2% of MMR-deficient cases. Well-differentiated tumours had a 76.5% proficiency rate as opposed to grade 2/3 disease with 53.2% and 52.9% proficiency rate respectively. There was no significant difference in MMR status when age 50 was used as a hypothetical testing threshold. After correcting for tumour grade, MLH1 and PMS2 expression was shown to be negatively correlated with age-at-diagnosis while MSH6 expression was positively correlated.

The investigators concluded that reflex MMR proficiency testing of all EEC cases is advisable, regardless of age, as using age 50 as a testing threshold would have missed 82.3% of MMR-deficient cases. Study conclusions supported several clinical improvement projects at Mater Dei Hospital (Malta), such as the introduction of a mismatch repair testing protocol. It also supports the setting up of a familial gynaecological cancer syndrome clinic to counsel patients with tumour characteristics that potentially represent heritable genetic susceptibility to cancer. In an era where focus is shifting to personalised treatment, targeted testing will pave the way towards personalised screening and management while empowering patients in a setting of comprehensive cancer care.