An Audit of MMR Immunochemistry in Endometrial Carcinomas in a Regional Cancer Centre

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Introduction

Universal screening for Lynch syndrome using MMR immunohistochemistry is recommended for all endometrial cancers following NICE guidance issued in October 2020. Guidance documents in interpretation of IHC are provided by the BAGP (June 2020)

Aims and Objectives

This audit aims to assess local testing outcomes including pickup rate for Lynch Syndrome and highlight challenges associated with accurate interpretation and interobserver variability.

Standards

Immunohistochemical staining for MLH1, PMS2, MSH2 and MSH6 to be performed in all endometrial cancers.

Germline mutation testing on all cases with MSH2, MSH6 or isolated PMS2 mutation.

Methylation testing followed by germline mutation testing (where appropriate) in all cases with loss of MLH1 or both MLH1 and PMS2 together.

MMR deficiency (dMMR) is expected in approximately 20-30% of endometrial carcinomas.

Methods

Interrogation of clinical and laboratory records covering a 12-month period yielded 338 cases of endometrial carcinomas that had undergone MMR immunohistochemistry.

This included cases submitted from across the Northeast and North Cumbria for central review. Samples included biopsy and resection specimens.

Results

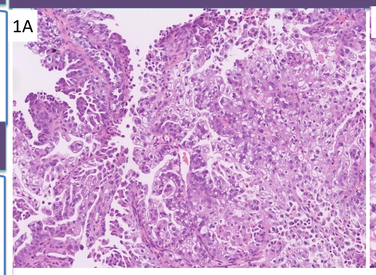
Seventy-seven cases (23%) show MMR deficiency of any type.

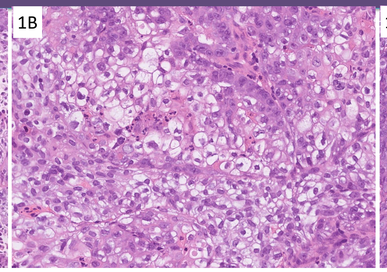
Of these, sixty-six cases (85%) showed MLH1 loss, with forty-six cases revealed the presence of MLH1 hypermethylation. Two cases showed germline mutations of MLH1.

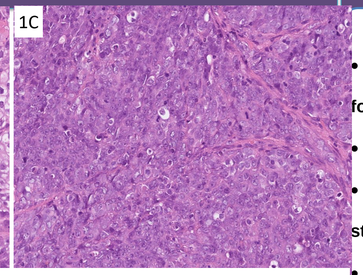
Thirteen cases display MSH6 loss and were referred directly to clinical genetics.

A total of four cases (1.2% [5.2%]) have been formally diagnosed as a Lynch or related syndrome with three cases awaiting further investigation.

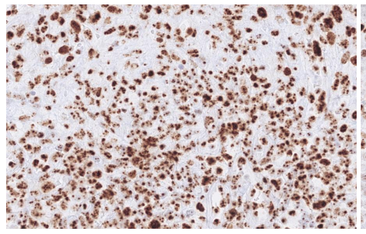
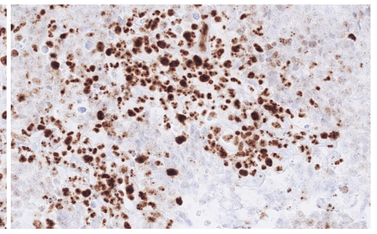
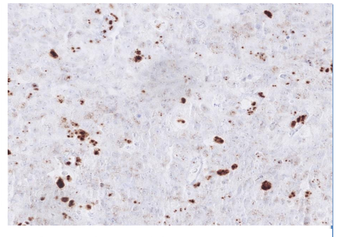
Of the dMMR cases, 32% showed heterogenous pattern of staining with interobserver variability and 5% were uninterpretable due to processing related issues.



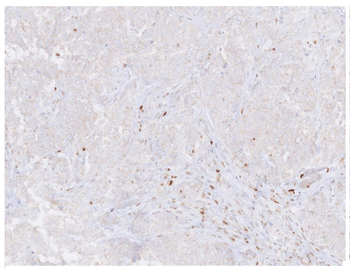




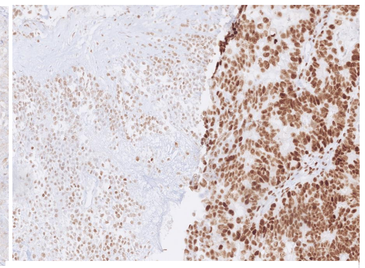
Architectural and cytomorphological heterogeneity in a difficult to classify high grade endometrial carcinoma from a 40yr old germline MLH1 pathogenic variant carrier

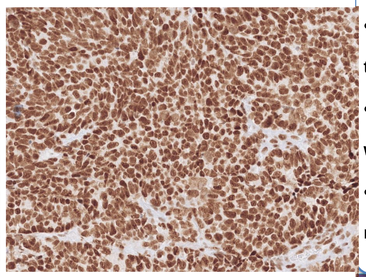
2A-2C. MLH1 loss with punctate nuclear expression. Different areas of same tumour shown in 1A-1C



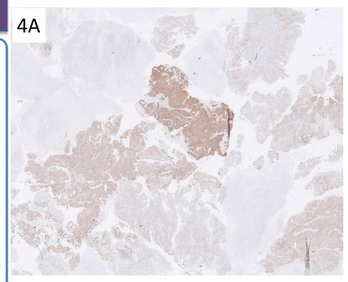
3A. Uniform loss of PMS2 staining of same tumour in figures 1A-1C

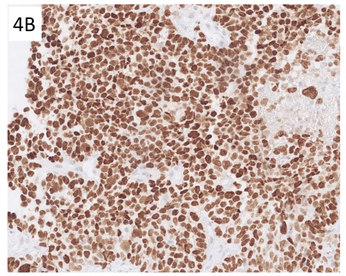


3B. Mixed intact and weak clonal staining with MSH6 ?artefact. Same tumour in 1A-1C



3C. Normal expression of MSH2 of same tumour in 1A-1C





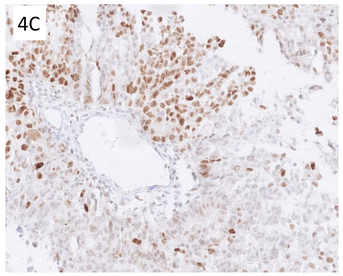


Figure 4A. Low power magnification showing variable p53 staining pattern
Figure 4B. High power image showing areas of aberrant p53 overexpression
Figure 4B. High power image showing areas of wild type/ normal p53 staining pattern

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Discussion

- **Local detection rates for dMMR EC is within the expected range. Local pick-up rates for Lynch Syndrome are below the median value (1.2% vs 3.2%)**
- **The specimen quality can have a significant effect on the quality of MMR IHC.**
- **Normal expression of MMR protein on IHC is regarded as a uniform, smooth nuclear stain which may be of varying intensity**
- **Fixation or other suboptimal preparations may lead to heterogenous, subclonal or punctate patterns of expression which are at risk for interobserver variability.**
- **While punctate staining in MLH1 is a known technical artefact associated with particular clones, we report cases with punctate staining in other markers, including PMS2 and MSH2**
- **We suggest that newer platforms for MSI testing with extended marker panels may be considered in the future as an alternative to subjective immunohistochemistry and reduce burden on pathologists**
- **Existing MSI assays have been shown to have concordance and similar pick-up rates to IHC, but are limited by cost, availability and technical requirements**
- **Newer methodologies may reduce the technical requirements, such as DNA quantity, while also providing greater sensitivity for pathological variants**
- **These include Multiplex PCR of biopsy and small volume specimens. Ongoing research shows promise in detecting pathological variants in shed samples**

Reference

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