AUDIT OF MMR PATHWAY FOR ENDOMETRIAL CARCINOMA

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BACKGROUND

- 25-30% of endometrial carcinomas are mismatch repair (MMR)-deficient. Out of these about 3 - 5% are associated with Lynch syndrome (LS) or related syndromes which involve mutation in 1 of the 4 MMR genes namely *MLH1, PMS2*, *MSH2* or *MSH6*.
- Screening for LS is important because endometrial cancer is frequently the first or sentinel malignancy in >50% of LS patients who develop cancer.
- It provides an opportunity for the early diagnosis of LS and enables colorectal surveillance, which has been shown to save lives through the detection and removal of premalignant polyps and earlier detection of invasive disease as well as the cascade testing for LS in other family members.
- In the United Kingdom, these potential benefits have been recognised and the National Institute of Clinical Excellence (NICE) has provided guidance for MMR testing for women with endometrial cancer.

OBJECTIVES

- The aim of the audit is to compare the whole of the MMR pathway at Birmingham Women's Hospital with the recommendation on the BAGP BGCS pathway[1] that provides practical interpretation of the NICE guidance DG42[2].

STANDARD

- The MMR pathway for endometrial carcinoma should follow the BAGP BGCS recommended pathway for implementation of the NICE diagnostic guidance which states that testing for Lynch syndrome should be offered when a person is diagnosed with endometrial cancer. Testing is done on tumour tissue by immunohistochemistry (IHC) followed by MLH1 promoter hypermethylation if indicated. If the results show that LS is likely, germline genetic testing should be offered.

METHODS

List of cases with diagnosis of endometrial carcinoma were retrieved for a 12 months period from January to December 2021 by TELEPATH search using endometrial and carcinoma as search criteria.

Data items that were collected include :

- total number of cases with diagnosis of endometrial carcinoma
- Numbers that were subjected for MMR IHC
- Numbers that expressed all markers
- Numbers showing loss of MLH1 and PMS2
- Numbers showing loss of MSH2 and MSH6
- Numbers showing isolated loss of PMS2
- Numbers showing isolated loss of MSH6
- Total cases sent for MLH1 promoter methylation testing
- Issuance of supplementary reports including results of the test
- Used of BAGP recommended terminology[3] for reporting MMR IHC
- Numbers referred to Clinical Genetic Services
- Numbers seen by Clinical Genetics Services
- Outcome of germline testing

RESULTS

- A total of 42 cases were included. The age distribution are as follows:

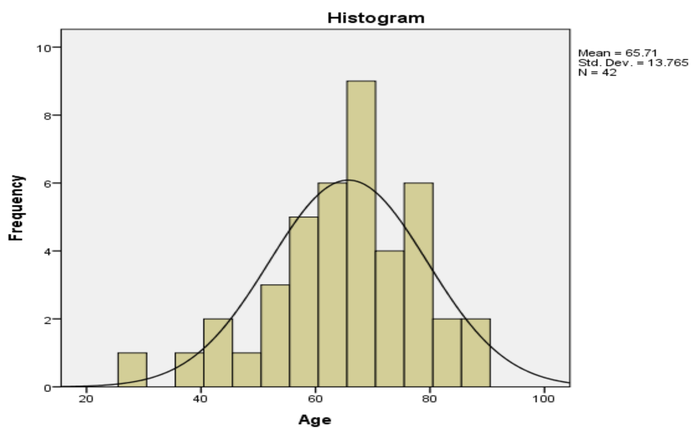

Figure 1 : Distribution of endometrial cases by age

Data	Results
• Histological type	Endometrioid carcinoma : 37/42 (88%) - Grade 1 : 22 - Grade 2 : 12 - Grade 3 : 3 Serous carcinoma : 5/42 (12%)
• Total cases that were subjected for MMR IHC	41 /42 (98%)
• All tested markers expressed	34/41 (83%)
• Used of recommended terminology for reporting MMR IHC	23/41 (56%)
• Loss of MLH1 and PMS2	6/41 (15%)
• Loss of MSH2 and MSH6	0/41 (0%)
• Isolated loss of PMS2	0/41 (0%)
• Isolated loss of MSH6	1/41 (2%)
• Total cases for MLH1 promoter methylation testing	6/6 (100%)
• MLH1 promoter methylation detected	3/6 (50%)
• MLH1 promoter methylation not detected	1/6 (17%)
• MLH1 promoter methylation : Analysis failed	2/6 (33%)
• Total numbers referred to Clinical Genetic Services	0/2

Table 1 : Results of the audit

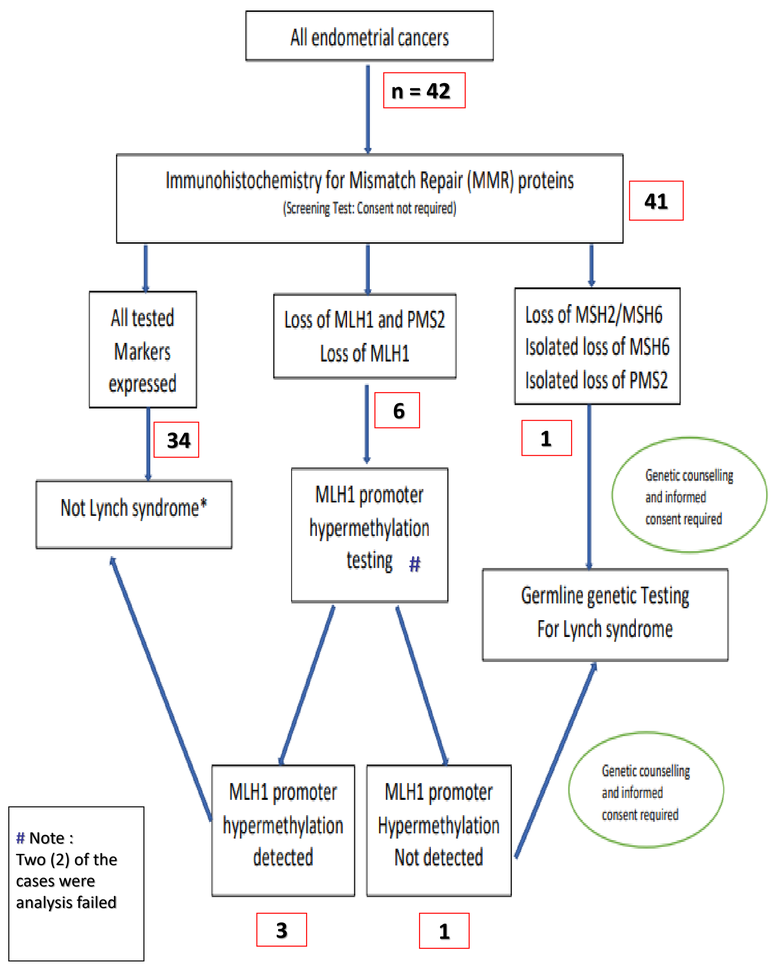

Figure 2 : Flow chart of the proposed pathway

DISCUSSION

- There was one case that was not tested for MMR IHC (histological diagnosis of serous carcinoma, p53 mutant), diagnosed in July 2021. The cause of the failure to test could not be ascertained. The MMR IHC was ordered after the audit and a supplementary report was issued.
- 23 out of 41 cases (56%) were compliant with the recommended terminology. All other cases included results of testing but had different and variable use of reporting terminology. MMR protein expression was retained in all these cases.
- The loss of MMR expression constituted around 2 of 41 tested cases. This is 4.8% of the tested cases and reflects the findings in literature.
- In 2 cases, MLH1 promoter methylation failed on the biopsy. One of these two women had a hysterectomy and MLH1 promoter methylation was done on this sample. The test result (promoter methylation detected) indicated that the loss of MLH1 expression was sporadic.
- Two cases (one showing isolated loss of MSH6; other showing loss of MLH1 and loss of promoter methylation) should have been referred to Clinical Genetic Services. On review of patient notes, there is no record of referral to genetics.
- In both these cases, the patient underwent subsequent hysterectomy. The MMR abnormality was not re-emphasised in the hysterectomy report.
- In both instances, the clinicians have been informed and requests have been made for referral.
- Strategies including re-emphasis at hysterectomy, notation at MDT and direct sharing of results with clinical genetics are being considered.

CONCLUSIONS

- The audit demonstrated almost full compliance for testing of MMR IHC but only reached 56% compliance for used of recommended terminology for reporting MMR IHC.
- Presentation of these findings and re-audit is planned.
- Auditing of the pathway has allowed me to understand the processes and pitfall with a view to implementing the pathway in Malaysia.

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REFERENCES

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2. NICE DG42 : https://www.nice.org.uk/guidance/dg42
3. BAGP Recommended MMR Terminology: https://www.thebagp.org/wp-content/uploads/download-manager-files/1593411202wpdm_BAGP%20MMR%20IHC%20Interpretation%20June%202020.pdf
4. Neil AJ Ryan, Dominic Blake, Marcus Cabrera-Dandy, Mark A Glaire, D Gareth Evans, Emma J Crosbie. The prevalence of Lynch syndrome in women with endometrial cancer : a systematic review protocol