Subclonal Mismatch Repair Protein Abnormalities in Endometrial Endometrioid Carcinoma: Association with POLE Mutation, p53 Immunohistochemistry, MLH1 Promoter Methylation, and Lynch Syndrome

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Background

- Accurate interpretation of mismatch repair (MMR) protein immunohistochemistry (IHC) in endometrial endometrioid carcinoma (EC) is essential for accurate molecular classification.
- Most tumors with MMR deficiency show complete protein loss (cMMR).
- Subclonal MMR protein loss (sMMR) is uncommon and complicates molecular
- sMMR may correlate with other molecular abnormalities such as *POLE* exonuclease domain mutation (*POLEedm*), complete MMR protein loss, subclonal p53 abnormalities, MLH1 promoter methylation, or Lynch syndrome (LS).

Aims and Methods

- Search Beaker EMR database for "subclonal" and "endometrial" from 2018-2024 to identify endometrial cancer cases with sMMR IHC
- Extract clinical and pathological information from EMR
- Correlate sMMR IHC with MLH1 promoter methylation (when relevant), *POLEedm* (when available), p53 IHC pattern, and Lynch syndrome status (when known)

Results

Mean Age (Range)	63.5 (38-91)	
Stage (FIGO 2009)	IA	22
	IB	10
	II	1
	III / IV	9
Diagnosis	FIGO 1 (Low Grade) Endometrioid	22
	FIGO2 (Low Grade) Endometrioid	19
	FIGO 3 (High Grade) Endometrioid	6
	De-differentiated carcinoma**	1
	Mixed* (EC + other)	3
Specimen Type	Biopsy	6
	Hysterectomy	26
	Both	16

820 samples from 662 patient with endometrial carcinoma
223 samples from 208 patients with any MMR abnormality
174 samples with diffuse MMR abnormality only

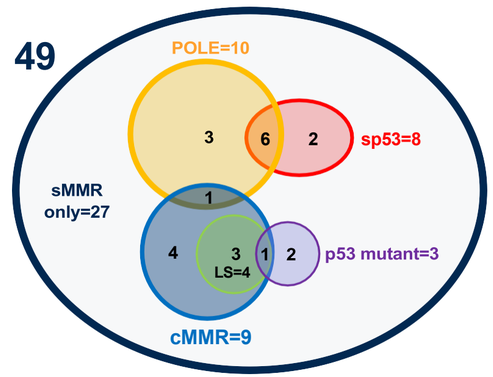
49 cases with sMMR (7.4% of EMCA)
- 38 cases (79.2%) with single complex loss
- 11 cases (20.8%) with combined complex loss
- 11 cases (20.8%) with mutant p53 IHC
  - Diffuse: 3 cases (27.3%)
  - Subclonal: 8 cases (72.7%)
- 10 cases with POLEedm mutation (20.4%)

sMLH1/sPMS2 (38 cases):
- 31 cases (81.5 %) with promoter hypermethylation
- 5 cases (13.1%) were non-methylated
- 2 cases not assessed
- If sPMS2, sMSH2/MSH6, sMSH6, no Lynch

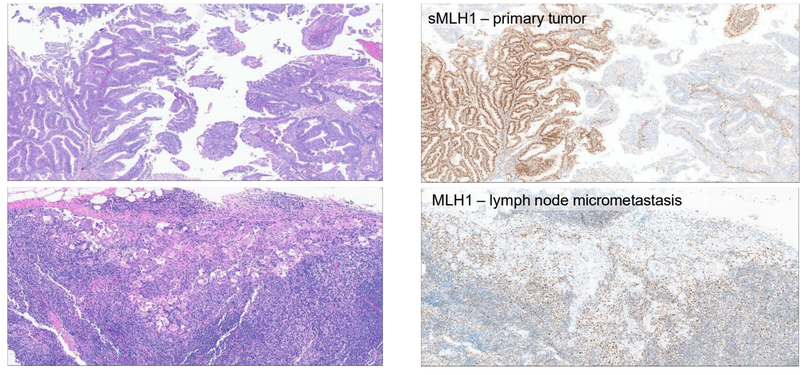
4 Lynch syndrome (LS) cases due to diffuse MMR abnormality, not subclonal abnormalities

	MMR PROTEIN(S) LOST	MLH1 Promoter Methylation	Lynch	p53	POLE
1	sMLH1 sPMS2	Methylated	No	NA	ND
2	sMLH1 sPMS2	Methylated	No	Wild type	ND
3	sMLH1 sPMS2	Non-Methylated	Testing Advised	Wild type	ND
4	sMLH1 sPMS2	Methylated	No	Wild type	ND
5	MLH1 PMS2 sMSH6	Non-Methylated	Yes - MLH1	Wild type	ND
6	sMLH1 sPMS2	Non-Methylated	No	Wild type	ND
7	PMS2 sMSH6	ND	Yes - PMS2	Missense Mutant	ND
8	sMLH1 sPMS2	Methylated	No	Subclonal Mutant	ND
9	sMLH1 sPMS2	Methylated	No	Wild type	ND
10	sMLH1 sPMS2	Methylated	No	Wild type	ND
11	sMLH1 sPMS2	Non-Methylated	No	Wild type	ND
12	sMLH1 sPMS2	Non-Methylated	Testing Advised	Wild type	ND
13	sMLH1 sPMS2	Methylated	No	Subclonal Mutant	Mutated
14	sPMS2	ND	No	Subclonal Mutant	Mutated
15	sMLH1 sPMS2	Methylated	No	Wild type	ND
16	MLH1, PMS2 sMSH6	Methylated	No	Wild type	ND
17	sMLH1 sPMS2	Methylated	No	Wild type	ND
18	sMLH1 sPMS2	Methylated	No	Subclonal Mutant	Mutated
19	sMLH1 sPMS2	Methylated	No	Wild type	Non-mutated
20	sMLH1 sPMS2	Methylated	No	Wild type	ND
21	sMLH1 sPMS2 *	Methylated	No	Wild type	Mutated
22	sMLH1 sPMS2 **	Methylated	No	Wild type	Non-mutated
23	MLH1 PMS2 sMSH6 sMSH2	Methylated	No	Wild type	Mutated
24	sMLH1 sPMS2	ND - 91 yo	No	Wild type	Non-mutated
25	sMLH1 sPMS2 sMSH6	Methylated	No	Wild type	Non-mutated
26	sMLH1 sPMS2	Methylated	No	Wild type	Non-mutated
27	sMLH1 sPMS2 MSH6	Non-Methylated	Yes - MSH6	Wild type	Non-mutated
28	sMLH1 sPMS2	Methylated	No	Wild type	Non-mutated
29	sMSH6	NA	No	Subclonal Mutant	Mutated
30	sMLH1 sPMS2 (metastasis is diffusely MLH1 deficient) *	Methylated	No	Mutant (diffuse nuclear and cytoplasmic)	Non-mutated
31	sMLH1 sPMS2	Methylated	No	Wild type	ND
32	sMLH1 sPMS2 *	Methylated	No	Subclonal Mutant	Non-mutated
33	sMLH1 sPMS2	Methylated	No	Wild type	Non-mutated
34	MLH1 sMSH6	Methylated	No	Wild type	Non-mutated
35	sMLH1	Methylated	No	Wild type	Non-mutated
36	sMLH1 sPMS2	Methylated	No	Wild type	Mutated
37	MLH1 PMS2 sMSH6	Methylated	No	Wild type	Non-mutated
38	sMLH1,PMS2,sMSH2,sSMH6	Methylated	Testing Advised	Wild type	Non-mutated
39	sMLH1 sPMS2	Methylated	No	Missense Mutant	Non-mutated
40	sMLH1 sPMS2	Methylated	No	Wild type	Mutated
41	MLH1, PMS2, sMSH6	Non-Methylated	Yes – MLH1	Wild type	ND
42	sMLH1, sPMS2	Methylated	No	Subclonal Mutant	Mutated
43	sMSH2, sMSH6	ND	No	Not Assessed	ND
44	sMLH1,sPMS2	Methylated	No	Wild type	ND
45	sMLH1, PMS2	Methylated	No	Wild type	Non-mutated
46	sMLH1, sPMS2	ND	No	Wild type	ND
47	sMLH1, sPMS2	Methylated	No	Wild type	ND
48	sMSH2, sMSH6	ND	No	Subclonal Mutant	Mutated
49	MLH1,PMS2, sMSH6	Methylated	No	Wild type	Non-mutated

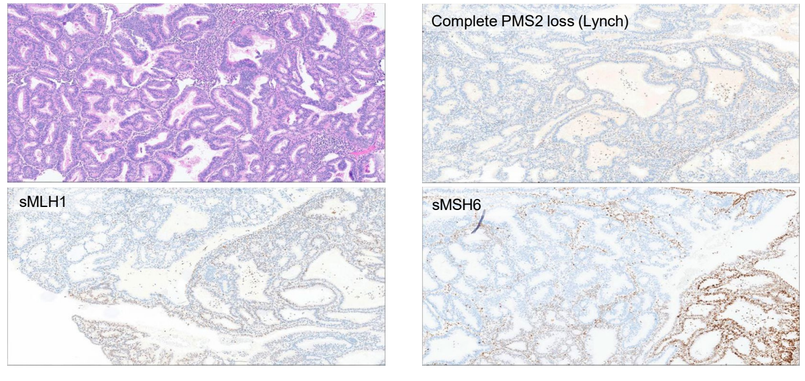
Overlap of Molecular Features with Subclonal MMR



Case 33: FIGO grade 1 sMLH1, deep myoinvasion, ++LVSI, MLH1-negative micrometastasis



Case 38: Lynch Syndrome: FIGO grade 1, complete PMS2 loss & sMLH1, sMSH2, sMSH6



Conclusion

- Most ECs with sMMR involve a single MMR protein pair, most often sMLH1/sPMS2, without MLH1 promoter methylation.
- 3 cases of Lynch syndrome identified were due to germline MSH6, MLH1, or PMS2 mutation, not the sMMR defect.
- This suggests that EC patients showing sMLH1/sPMS2 alone may not need MLH1 promoter methylation testing or Lynch syndrome screening.
- *POLEedm* status is frequently observed in tumors with sMMR and subclonal mutant p53 IHC. For institutions not doing universal *POLE* testing, this suggests sMMR and/or sp53 should prompt *POLEedm* testing.

References

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