Characterization of atypical dMMR (deficient MisMatch Repair) tumors: a study from a large cohort of 4948 cases.

Janick Selves, Marion Jaffrelot, Anne Pascale Laurenty, Samira Icher, Nadim Farés, Anne Cécile Brunac, Marie Danjoux, Julie Meilleroux, Christine Toulas, Edith Chipoulet, Rosine Guimbaud
MMR system = MisMatch Repair

DNA Mismatch Repair system

Mismatches: microsatellites

4 proteins, Functional heterodimers:
- MSH2/MSH6
- PMS2/MLH1

dMMR: role in oncogenesis

Microsatellite stability (MSS)  
Microsatellite Instability (MSI)
Indications for somatic MMR testing:

Lynch syndrome screening

Prognosis factor for Colorectal and (gastric, endometrial) cancer: (neo) adjuvant chemotherapy?

All M+ cancers: anti PD1/PDL1 Immunotherapy Clinical trials ++

Increasing of the indications ++
Not only colorectal / endometrial cancers
Methods used in clinical practice

<table>
<thead>
<tr>
<th>Molecular Biology (MB)</th>
<th>Immunohistochemistry (IHC)</th>
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</thead>
<tbody>
<tr>
<td>• <strong>MSI high</strong> : instability ≥ 2 microsatellites</td>
<td>Testing 4 MMR proteins MLH1/PMS2, MSH2/MSH6:</td>
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<tr>
<td>• <strong>MSI low</strong> : 1 unstable microsatellite</td>
<td>Retained staining: pMMR</td>
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<tr>
<td>• <strong>MSS</strong> : 5 stable microsatellites</td>
<td>Loss of protein staining: dMMR</td>
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<tr>
<td>[Pentaplex PCR, NCI panel (1)]</td>
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**Sensitivity / Concordance:**

- **IHC**: *sensitive* (92.3%), very *specific* (100%) (2)
- **Concordance IHC/ MB**: 95 to 99% (3, 4)

(1) Xicola RM et al. J Natl Cancer Inst. 2007
(2) Lindor NM et Al. J Clin Oncol. 2002
(3) Cicek MS et Al.. J Mol Diagn. 2011
The dMMR profiles

**Classical pattern**

**MSI-H**

Coupled loss of proteins:
- MLH1/PMS2
- MSH2/MSH6

**MB**

**IHC**
The dMMR profiles

**Classical pattern**
- **MSI-H**
  - Coupled loss of proteins: MLH1/PMS2, MSH2/MSH6

**Atypical patterns**
- **MSS**
  - Loss of protein
- **MSI-H**
  - No coupled loss of protein
  - Or retained 4 proteins
- **MSI LOW**
Materials & Methods

• All MMR testing performed between 2007 and 2017
• Cancer Molecular Biology Platform of Midi-Pyrénées

2007
Colo-rectal cancers
• 1511 analyses
• 1462: both IHC + MB analyses (97%)

2012

2017
All cancers
• 3437 analyses
• 2338: both IHC + MB analyses (68%)

N = 4948
Of which
3800 IHC + MB
Materials & Methods

- All MMR testing performed between **2007 and 2017**
- **Cancer Molecular Biology Platform** of Midi-Pyrénées

### Colo-rectal cancers

- 1511 analyses
- 1462: both IHC + MB analyses (97%)

### All cancers

- 3437 analyses
- 2338: both IHC + MB analyses (68%)

**Total:**
- 585 dMMR
  - Of which 97 atypical
- 395 dMMR
  - 81 atypical

N = 4948
- Of which 3800 IHC + MB
Results (n = 97 atypical dMMR)

- 67% Colorectal cancer (CRC)
- 14% GI cancers (no CRC)
- 11% Endometrial carcinoma
- 8% Other tumor types
Controls of the analyses (n = 90/97)

19 reclassified cases (21%)

- n = 6 (35.2%): IHC repeated on the same block
- n = 7 (36.8%): IHC on initial slides reviewed
- n = 2 (10.5%): IHC repeated on a different block
- n = 2 (10.5%): Initial MB reviewed
- n = 2 (10.5%): Repeated MB on a different block

After reviewing: **8 cases were reclassified as typical** (5 colons, 3 endometrium)
**89 atypical dMMR cases were confirmed = 15%**
Results (n = 89 atypical dMMR)

- PMS2 or MSH6: Isolated loss (n = 53)
- Classical coupled loss of two proteins (n = 16)
- Retained expression of 4 proteins (n = 5)
- Aberrant loss of protein expression (n = 15)

- 43 MSI-H
- 1 MSI low
- 9 MSS

- 3 MSI-H
- 2 MSI low
- 2 MSS

- 8 MSI low
- 8 MSS

43 cases with a known biological mechanism = « atypical already described » (1,2)

46 cases: « true atypical »

(1) Alpert L et Al. Arch Pathol Lab Med. Apr 2018
(2) Daria Carmela Loconte et Al. Human Pathology. 2014
Results (n = 89)

PMS2 / MSH6 isolated loss n = 53
- 43 MSI-H
- 1 MSI low, 9 MSS
- 38 CCR / endometrium

73 % genetic syndromes
Lynch ++, 1 Pol-E, 1 CMMR-D
Results (n = 89)

PMS2 / MSH6 isolated loss n = 53

- 43 MSI-H
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73 % genetic syndromes
Lynch ++, 1 Pol-E, 1 CMMR-D

Retained 4 proteins n = 5

- 3 MSI-H (2 Lynch)
- 2 MSI low

Exceptional Missense mutation ++
Results (n = 89)

- **PMS2 / MSH6 isolated loss** n = 53
  - 43 MSI-H
  - 1 MSI low, 9 MSS
  - 38 CCR / endometrium
- **Classical MMR coupled loss** n = 16
  - 8 MSI low, 8 MSS
- **RARE**
  - False negative Pentaplex PCR?
  - Mainly no colorectal cancer: 63% of cases

- **Retained 4 proteins** n = 5
  - 3 MSI-H (2 Lynch)
  - 2 MSI low

- **73% genetic syndromes**
  - Lynch ++, 1 Pol-E, 1 CMMR-D

- **Exceptinal**
  - Missense mutation

- **Main colorectal cancer (CRC)**
  - 20%
- **GI cancers (no CRC)**
  - 80%
- **Endometrial carcinoma**
- **Other tumor types**
Results (n = 89)

PMS2 / MSH6 isolated loss n = 53
- 43 MSI-H
- 1 MSI low
- 9 MSS
- 38 CCR / endometrium

73 % genetic syndromes
Lynch ++, 1 Pol-E, 1 CMMR-D

Classical MMR coupled loss n = 16
- 8 MSI low
- 8 MSS

RARE
False negative Pentaplex PCR ?
Mainly no colorectal cancer : 63% of cases

Retained 4 proteins n = 5
- 3 MSI-H (2 Lynch)
- 2 MSI low

Exceptional
Missense mutations ++

Aberrant loss of protein n = 15
- 13 MSI-H
- 2 MSS

MSI ++ : complex mechanism of MMR inactivation ?
4 proteins loss : MLH1 methylation MLH1 + secondary inactivation of MSH6 or MSH2 (1)
Take home messages

• **All atypical results (MB and/or IHC) must be controlled** : to repeat or complete the analyses

• **8% of cases (MB + IHC) are atypical dMMR tumors**
  Increasing for non colorectal cancers
  
  Strong diagnosis value for Lynch syndrome or genetic syndromes

• **Biological and therapeutic value ?**
  Need to better characterize atypical dMMR cases :
  • Extensive sequencing on going
  • Therapeutic impact for immunotherapy ?
Thank you for your attention!