Envoi SPECIALIST PATHOLOGISTS *inside insights*

Update No.10 - 2016 *Dr Christophe Rosty*

The diagnosis of Lynch Syndrome

Definitions

***Lynch Syndrome*:** Genetically defined by the identification of a deleterious germline mutation in a DNA mismatch repair gene (*MLH1*, *PMS2*, *MSH2*, *or MSH6*) or in *EPCAM* gene; autosomal dominant inheritance.

***HNPCC (Hereditary Non-Polyposis Colorectal Cancer)*:** Clinically defined when a patient fulfils Amsterdam Criteria – ≥3 relatives with CRC in ≥2 successive generations and ≥1 CRC diagnosed <50 years; may or may not be Lynch syndrome.

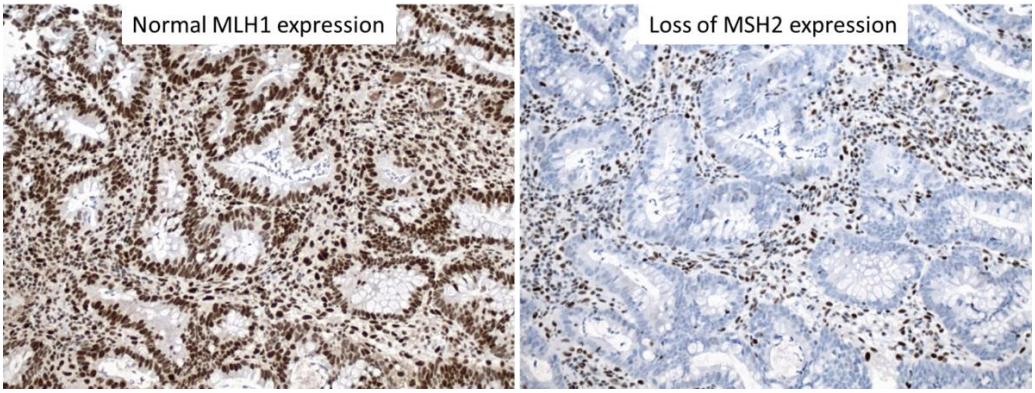
Mismatch Repair (MMR) Deficiency: Loss of expression of 1 or more MMR proteins by immunohistochemistry (IHC).

***Microsatellite Instability (MSI)*:** Abnormal number of short repeated DNA sequences (microsatellites) secondary to impaired DNA MMR mechanism; determined by molecular testing.

Interpretation of MMR protein expression by immunohistochemistry

Loss of IHC staining	Most likely cause	Patient management
No loss		Nil
MLH1 and PMS2	*MLH1* gene alteration • Somatic methylation (sporadic) • Germline mutation (familial)	Test for tumour *BRAF* mutation • Mutation present – sporadic; no further investigation • Mutation absent – possible Lynch syndrome*
MSH1, MS2, and MSH6	*MLH1* gene alteration and superimposed somatic mutation of *MSH6*	As for MLH1 and PMS2 loss
PMS2	*PMS2* gene alteration	Possible Lynch syndrome*
MSH2 and MSH6	*MSH2* or *EPCAM* gene alteration	Possible Lynch syndrome*
MSH6	*MSH6* gene alteration	Possible Lynch syndrome*

*In case of possible Lynch syndrome, genetic counselling and MMR gene testing are recommended



Comments and caveats

- Normal MMR expression can be determined by IHC using either only *PMS2* and *MSH6* or all 4 MMR proteins.
- *MLH1/PMS2* loss in patients ≥70 years are usually considered sporadic cases. *BRAF* mutation testing is recommended only when there is strong clinical suspicion of Lynch syndrome.
- Some cases with *PMS2* loss are caused by *MLH1* gene alteration.
- Some cases with *MSH6* loss are caused by *MSH2* gene alteration.
- Abnormal *MSH6* expression can occur secondary to radiotherapy (rectal cancer).
- "**Lynch-like syndrome**" is used when there is loss of MMR protein expression suggestive of Lynch syndrome but no MMR gene mutation is identified. This can be due to an undetectable germline mutation (Lynch syndrome) or to bi-allelic somatic mutations (not Lynch syndrome). Management is similar to cases of definite Lynch syndrome.
- Normal MMR expression does not completely exclude Lynch syndrome, in particular for *MSH6* mutation.

Testing for MMR deficiency using immunohistochemistry and colorectal polyps

- Indications for testing of adenomas for MMR deficiency are 1) patient fulfils Amsterdam criteria or 2) members of known Lynch syndrome family.
- Very little benefit for patients with adenomas <40 years, or those with CRC in first degree relative only
- Abnormal IHC is seen in 80% of adenomas in known Lynch syndrome patients. This rises to nearly 100% if high grade dysplasia and/or a villous component is present. A normal IHC result does not exclude Lynch syndrome.
- If strong familial context suggestive of Lynch syndrome, better to screen relatives with CRC or other Lynch syndrome-associated cancers rather than patients with polyps only

- **NO ROLE for testing for MMR deficiency in serrated polyps (including hyperplastic polyps, sessile serrated adenoma or traditional serrated adenoma) to identify Lynch syndrome.**

Further reading

1. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999; 116: 1453-6.
2. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014; 109: 1159-79.
3. Buchanan DD, Rosty C, Clendenning M, et al. Clinical problems of colorectal cancer and endometrial cancer cases with unknown cause of tumor mismatch repair deficiency (suspected Lynch syndrome). Appl Clin Genet. 2014; 7: 183-93.
4. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012; 308: 1555-65.
5. Ferreira S, Claro I, Lage P, et al. Colorectal adenomas in young patients: microsatellite instability is not a useful marker to detect new cases of Lynch syndrome. Dis Colon Rectum 2008;51:909–15.
6. Walsh MD, Buchanan DD, Pearson SA, et al. Immunohistochemical testing of conventional adenomas for loss of expression of mismatch repair proteins in Lynch syndrome mutation carriers: a case series from the Australasian site of the colon cancer family registry. Mod Pathol 2012;25:722–30.
7. Buchanan DD, Clendenning M, Rosty C, et al. Tumour testing to identify Lynch syndrome in two Australian colorectal cancer cohorts. J Gastroenterol Hepatol. 2016 Jun 6.