

It All Stays in the Family...

Lynch Syndrome Symposium
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Case presentation

- 12 yr old female, Ashkenazi origin

Past Medical History

- Age 6 yrs: mediastinal T cell lymphoma
- Age 11 yrs: rectal bleeding - sigmoidoscopy - 10 small tubular adenomas LGD

Family History

- Healthy parents, non consanguineous
five healthy siblings
- Paternal GGM died CRC, age 60
- Mother's 1st cousin endometrial cancer
age 47

childhood lymphoma
+
colonic tubular adenoma

and
café au lait spots



**biallelic mismatch repair
gene mutation?**

Genetic evaluation

- Founder *hMSH2* – normal
- Founder *hMSH6* – c.3984_3987dup
- *hMSH6*- biallelic mutation

1. c.3984_3987dup
2. c.3959_3962del



Compound heterozygous MMR-Deficiency
C-MMRD

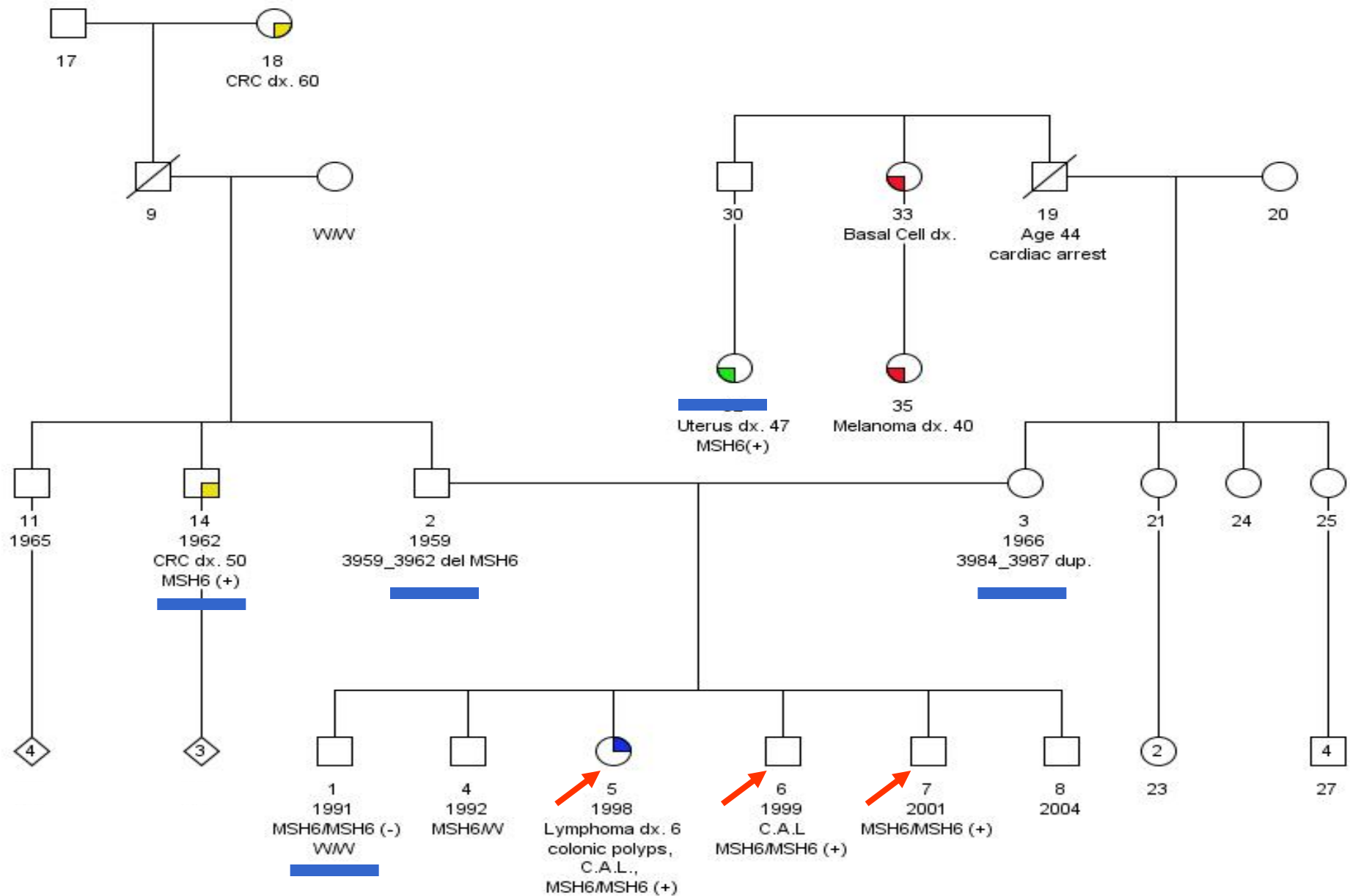
Colorectal Cancer Uterus

Lymphoma

Skin

Lynch syndrome

Biallelic C-MMRD



Monoallelic *hMSH6* mutations

- Mutation c.3984_3987dup* develop cancer at a mean age 61.
- Risk for malignancy: 33% by 60 yrs
84% by 80 yrs
- Tumor spectrum:
colon, gastric, ovarian, endometrial, urinary
- c.3959del4- no specific details

C-MMRD

- Biallelic carriers may develop cancer before their parents
- Typically little family history

C-MMRD

Recognized since 1999; characterized by:

- Childhood malignancies- lymphomas, leukemia, brain tumors or GIT cancers
- phenotype neurofibromatosis type 1
mostly café au lait spots, skin fold freckling
- Typically Amsterdam (-) and most Bethesda (-)

Cancer risk in 92 MMRD patients

	<u>Median age</u>
■ Hematologic: NHL (n=19), ALL (n=6), AML(n=3), unspecified (n=3)	6 (0.4-17)
■ Brain (glioblastomas, astrocytomas, medulloblastoma) (n=32)	8 (2-35)
■ Colorectal (n=37)	16 (8-35)
■ small bowel (n=9)	26 (11-42)
■ Endometrial (n=5)	24 (23-31)

Other cancers described in C-MMRD

	<u>Median age</u>
■ Ureter, renal pelvis	15
■ Neuroblastoma	13
■ Wilm's tumor	4
■ Rhabdomyosarcoma	4
■ TCC bladder	21
■ Breast cancer	35

* 30% more than one tumor

Management

- 102 individuals have been described
- Due to small number: no established evidence based guidelines

Expert recommendations for surveillance

biallelic MMR Carriers

Cancer

Surveillance

■ Children

Colon

colonoscopy annually

Upper GI and SB

EGD annually

video capsule annually

Brain

US at birth then MRI at 6mo

Leukemia/lymphoma

CBC, SR, LDH at 4 mo

■ Adults

Endometrium

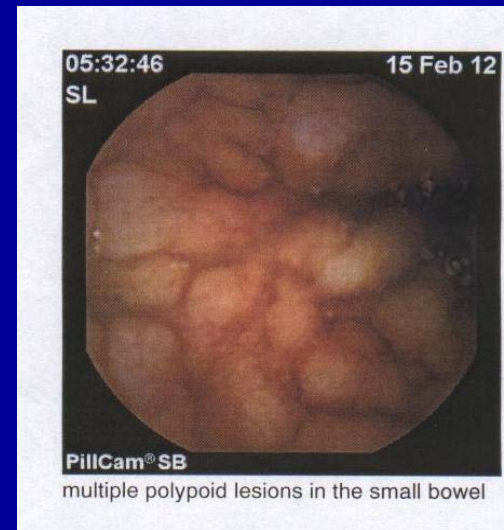
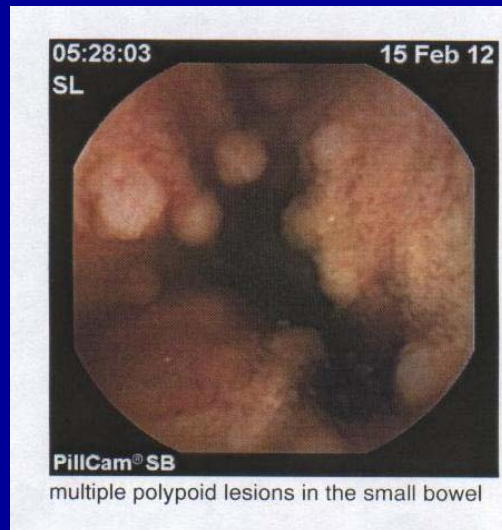
US annually

Urinary

US annually

Patient #5

- 14 yrs with history of T cell lymphoma
- Multiple CRC adenomas, one with HGD!
- SB capsule endoscopy: significant lymphoid hyperplasia (per biopsy)



Patient #5

- Brain MRI- small rt subcortical frontal lesion
DD tuberous or cortical dysplasia

————→ total proctocolectomy IPAA
follow brain MRIs

- Surveillance of small bowel due to lymphoid hyperplasia is difficult ??
Double balloon enteroscopy?

Patient #6

- 12 yrs
- CAL spots
- 6 TA small removed
- Lymphoid hyperplasia
- Asymmetry of sphenoid bone- no change
- Small gallbladder polyps < 1 cm

→ Cholecystectomy ??

Summary

- C-MMRD should be suspected in any child with a malignancy and :
 1. Café au lait spots
 2. Family history of consanguinity
 3. Family history of Lynch associated cancers in distant relatives
 4. Second malignancy
 5. Sibling with childhood cancer.
- Intense surveillance shown to increase survival in a selected kindred.
- Surveillance should be individualized.
- Molecular diagnosis: diagnosis of a lynch syndrome family.

Questions

- Small bowel surveillance in the setting of lymphoid hyperplasia- Capsule endoscopy? MRE? double balloon?
- Cholecystectomy?
- Is screening spouses of Ashkenazi HNPCC carriers warranted?
- Chemoprevention? Aspirin?

"כל המשפחות המאושרות דומות זו לזו. אך
המשפחות האומללות, אומללות הן כל אחת על פי
דרכה"

"Happy families are all alike. But unhappy
families are unhappy each in their own way"
Anna Karenina, Tolstoy 1877.

THANK YOU!!!!