Curr Probl Cancer 38 (2014) 249–261

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Hereditary colorectal cancer: More common than you think

Kory W. Jasperson, MS, CGC

Introduction

It is estimated that more than 20% of all colorectal cancers (CRCs) have a familial component, and up to 6% of cases are due to a known high-risk hereditary syndrome.[1] It is imperative that health care providers keep abreast of the genetics of CRC, as 1 in 5 patients with CRC walking through their office door may need referral for genetic counseling. Despite the well-documented benefits of increased screening and risk-reducing interventions in hereditary CRC syndromes, many remain undiagnosed. Reviewed here are novel and proven strategies to identify patients at risk for hereditary CRC syndromes, with a focus on Lynch syndrome (LS) and universal tumor testing of all CRCs, familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP). In addition, a case-based approach is used to highlight diagnostic pitfalls and successful interventions, including early cancer detection and prevention opportunities in families affected by a hereditary CRC syndrome.

Case 1

An otherwise healthy 54-year-old woman presents with a 2-month history of postmenopausal vaginal bleeding. She subsequently is diagnosed with stage IIA endometrial cancer (EC) and undergoes a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The hospital at which she was diagnosed recently implemented a testing protocol to routinely evaluate all ECs for LS. This testing protocol includes immunohistochemistry (IHC) analysis using MLH1, MSH2, MSH6, and PMS2 antibody staining on all surgically resected ECs, regardless of the age of onset or family history (this is also referred to as universal tumor testing). IHC analysis revealed absent MSH6 staining and normal staining of MLH1, MSH2, and PMS2. Given the abnormal IHC result, the patient was referred for genetic counseling and testing.

Cancer risk assessment and testing

During her genetic counseling appointment, a detailed family history was obtained as outlined in Figure 1. Her 59-year-old sister was diagnosed with ovarian cancer at the age of 58 years. This sister had undergone comprehensive *BRCA1* and *BRCA2* genetic testing the previous year, and no mutations

http://dx.doi.org/10.1016/j.currproblcancer.2014.10.005

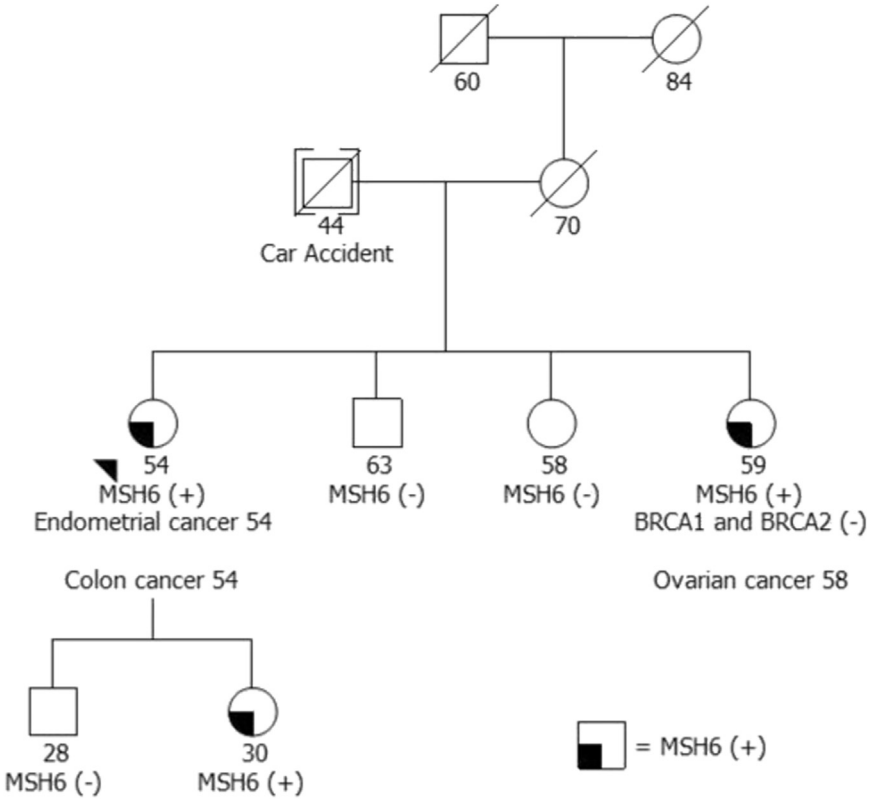

Fig. 1. Personal and family history of cancer and genetic test results for case 1 with Lynch syndrome.

were identified. The remainder of the family history was unremarkable, though her father died in an auto accident at a young age. In addition, he was adopted, and no information was available regarding his side of the family.

Owing to the patient's abnormal IHC test result, genetic testing of the *MSH6* gene was performed. This revealed a deleterious mutation, confirming a diagnosis of LS in the patient. Additionally, genetic testing for the known *MSH6* mutation was offered to her at-risk relatives, including her siblings and children. The results and implications of further testing in this family are outlined in the following sections.

Familial implications

The patient underwent a screening colonoscopy 4 years ago at the age of 50 years, and no polyps were found. The typical recommendation would have been for her to undergo a follow-up colonoscopy in 10 years. However, given her new diagnosis of LS, a repeat colonoscopy was performed, and she was found to have a stage IA cecal mucinous adenocarcinoma. She was recommended to undergo right hemicolectomy but was also given the option of total colectomy with ileorectal anastomosis owing to the increased risk of metachronous CRC in LS. She elected total colectomy with ileorectal anastomosis.

Lynch syndrome

LS, also known as hereditary nonpolyposis colorectal cancer, is an autosomal dominant condition caused by a germline mutation in one of the mismatch repair genes (*MLH1*, *MSH2*,