

Muir Torre syndrome and in vitro fertilization: One family's experience



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INTRODUCTION

Lynch syndrome is caused by autosomal-dominant germline mutations in DNA mismatch repair genes. Five genes have been identified (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*)¹ with mutations in *MLH1*, *MSH2*, and *EPCAM* causing the most severe phenotypes. Malignancies develop as further somatic mutations occur, resulting in loss of heterozygosity and genomic instability.² The 2 most common cancers seen are colorectal and endometrial carcinomas, although these patients are at increased risk for many other internal malignancies.³ Muir Torre syndrome (MTS) is a rare, phenotypic subtype of Lynch syndrome defined by the development of at least 1 cutaneous sebaceous neoplasm and one internal malignancy.⁴ These sebaceous neoplasms include adenomas, epitheliomas, carcinomas, and Fordyce spots of the oral mucosa.^{4,5} Multiple keratoacanthomas can also occur, and cutaneous manifestations can precede, occur concomitantly, or present years after internal malignancy.⁴ Current recommendations for patients with this diagnosis include frequent cancer screenings and genetic testing of first-degree relatives. This action can lead to multiple family members receiving the diagnosis in short succession and physicians educating entire family units. Many patients desire biological children and wish to know what measures are available to prevent passing on their mutation.

CASE REPORT

A 57-year-old woman with a medical history of Lynch syndrome with associated colon cancer and metastatic endometrial cancer, presented to the dermatology clinic for a slowly growing bump in her right axilla that bled intermittently. Physical

Abbreviations used:

IVF: in vitro fertilization
MTS: Muir Torre syndrome
PGD: preimplantation genetic diagnosis
PGT: preimplantation genetic testing

examination found a firm, smooth, dome-shaped, pink papule with apical ulceration. Shave biopsy and histopathologic examination found a sebaceous carcinoma, further classifying her diagnosis as MTS. After discussion of treatment options, the patient elected for Mohs micrographic surgery followed by clinical surveillance.

At the time of this patient's Lynch syndrome diagnosis, thorough personal and family medical histories were obtained, revealing breast cancer in her mother and pancreatic cancer in a maternal aunt. She had 7 seemingly unaffected siblings and 4 healthy children in their 20s to 30s.

The diagnosis was confirmed through identification of a mutated *MLH1* gene, resulting in a severe phenotype. Undergoing partial colectomy for colorectal carcinoma, total hysterectomy with bilateral salpingo-oophorectomy for endometrial carcinoma, and prolonged chemotherapy for metastatic disease has taken a substantial toll. The inherent pain and side effects of these treatments along with the constant threat of future malignancies have caused significant psychologic distress for the patient and her family.

This fear was compounded when first-degree family member testing found identical mutations in several relatives. One such relative additionally learned that her newborn child also carried the mutation, who was conceived via in vitro fertilization

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(IVF). This individual had several other embryos in cryopreservation and found herself in the unique position of dealing with a devastating diagnosis for herself and her first child, with the capability of preventing this fate for her future children. When she and her partner desired a second child, a stored embryo was thawed, biopsied, tested, and found to be positive for the mutation. The couple chose not to implant this embryo, and instead repeated this process on another embryo, which was found to be negative for the mutation and subsequently implanted. The couple delivered this child and continue to cryopreserve several additional, untested embryos.

DISCUSSION

The number of patients seeking reproductive assistance and the technology behind it has grown exponentially since the first live human IVF birth in 1978.⁶ The protocol involves ovarian stimulation with hormonal modulators followed by oocyte retrieval with ultrasound-guided transvaginal needle aspiration.⁷ Next, the oocytes are fertilized with sperm and grown in culture for 3 to 5 days, at which point the intended parent(s) can elect for trophectoderm biopsy with preimplantation genetic testing (PGT). After PGT, the embryos are frozen and later transferred into the uterus when receptivity is deemed to be optimal based on natural or exogenous hormone-induced endometrial thickening.⁷ Of note, investigators have found that parous women have lower risk of endometrial carcinoma development related to Lynch syndrome than nulliparous women, alleviating the concern that elevated hormones of gestation may induce carcinogenesis.^{8,9}

PGT is an umbrella term that includes both preimplantation genetic screening, offered to all IVF patients to identify aneuploidy, and preimplantation genetic diagnosis (PGD), to identify specific gene mutations when one or both of the parents are known carriers. PGD can currently identify hundreds of genetic mutations with implications ranging from benign to lethal.¹⁰ One major ethical concern with this technology is what happens to the embryos that display mutations; currently, that choice is left to the intended parent(s). Most choose not to implant embryos with serious genetic anomalies, electing instead to cryopreserve, discard, or donate them for scientific research.¹¹ However, some will implant these embryos because only one was produced, the patient's religious beliefs dictate equal respect and opportunity to all life, or the intended parent wishes for the child to experience the condition.¹⁰

Some religious and ethical belief systems have major moral concerns with IVF and/or PGT. Any

perceived physician partiality toward or against its use may offend or alienate patients with these beliefs. Some are wholly against any medical intervention in procreation, whereas others condone IVF but believe that genetically selecting embryos devalues the lives of individuals with heritable conditions. Some affected parents may even view their condition as a defining part of their identity and cultural experience, desiring their children to share this worldview. Therefore, dermatologists should have an accurate understanding of the terminology and methodology involved in IVF and PGT to educate patients seeking information, but referral to a genetic counselor or bioethicist may be more appropriate for in-depth counseling on the pros and cons.

CONCLUSION

MTS is a genetic cancer syndrome that requires multigenerational education by physicians. IVF with PGD offers patients the ability to conceive biological children with low risk of inheriting the disease. Although selecting embryos genetically can be controversial depending on individual religious and ethical belief systems, the American College of Medical Genetics and Genomics considers providing complete and accurate information on management options the legal and ethical responsibility of doctors.¹² Therefore, health care professionals should have the knowledge to inform their patients on this technology when appropriate.

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