A rare pseudomyxoma peritonei with a *MSH2* variation of unknown significance and two mutation carrier family members

Yoo Min Kim¹ and Min Kyu Kim^{2,*}

¹Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

²Department of Obstetrics and Gynecology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Pseudomyxoma peritonei (PMP) is a rare tumor that usually originates in the appendix, but a small number of cases originate in the ovary. Lynch syndrome (LS) is an autosomal dominant hereditary condition that increases the risk of cancer, particularly in the colon and endometrium. Mutations in the mismatch repair genes (*MSH2*, *MLH1*, *MSH6*, and *PMS2*) increase the risk of LS. Reported PMP cases with hereditary gene mutations of unknown significance are also rare. Here, we investigated a PMP patient and her family members, who have an *MSH2* variant of unknown significance. Physicians have an important role in counseling, management, and surveillance based on genetics and pathogenicity.

Key words: Pseudomyxoma peritonei, Lynch syndrome, Germ-line mutation.

Introduction

Pseudomyxoma peritonei (PMP) is known to originate in the appendix and peritoneal tissue, including the ovary. The pathogenesis of PMP is less understood than that of colon and ovarian cancer. Lynch syndrome (LS), or hereditary nonpolyposis colorectal cancer (CRC), is characterized by mutations in the mismatch repair (*MMR*) genes and by its development in multiple extracolonic sites (mostly endometrium) [1-3]. LS accounts for approximately 3-5% of CRCs; patients with LS have a 60-80% lifetime risk of CRC [4,5]. The appendix is a small organ connected to the cecum, connecting the small and large intestines. PMP and LS have not been studied extensively owing to their rare occurrence [6]. However, identifying a germline mutation carrier has a prophylactic advantage of better

predicting secondary and primary cancer in family members of the patient. Contrary to reported germline mutations, the interpretation of variants of unknown significance (VUS) and establishment of proper guidelines for counseling VUS patients poses a challenge. We report a rare case of PMP with a *MSH2* VUS transmitted to her family, and counseling for the patient and her carrier children.

Case

A 60-year-old woman presented to a local hospital with vaginal spotting, which had been occurring for 1 week.

An approximately 10-cm pelvic mass was found by pelvic ultrasound, and she was transferred to the Samsung Changwon Hospital (Changwon, Korea) in 2014 for further evaluation.

Received: 2 February 2016, Revised: 3 March 2016, Accepted: 14 March 2016, Published: 30 June 2016

*Corresponding author: Min Kyu Kim, M.D., Ph.D.

Department of Obstetrics and Gynecology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea.

Tel: +82-55-290-6040, Fax: +82-2-6442-9285, E-mail: minkyukim@skku.edu

Conflict of interest: The authors declare that they do not have any conflicts of interest.

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

© Copyright 2016 by the Korean Society of Medical Genetics

www.e-kjgm.org

Under the impression of gynecologic malignancy, further workups, including esophagogastroduodenoscopy, colonoscopy, abdominal computed tomography (CT), and analysis for tumor markers, were performed. The abdominal CT revealed a 9-cm cystic mass in the peritoneal cavity (Fig. 1A), intraperitoneal ascites, and omental infiltrations. CA 125 was elevated at 58.15 U/mL (normal range <35 U/mL).

During laparotomy, we found an abundance of gelatinous ascites in the pelvic cavity, a 10-cm mass in the left ovary, a 5-cm mass in the right ovary containing mucin, and a swollen appendix with atypical features measuring 5 cm in length and 1 cm in diameter (Figs. 1B and C). Frozen biopsy pointed to a suspected malignancy in the appendix and ovary. For surgical staging, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, total omentectomy, right hemicolectomy, diaphragm, and peritoneal stripping were performed. The final histological report showed a PMP low-grade mucinous neoplasm originating from the appendix (Fig. 1D), and metastatic sites in both ovaries, the omentum, ascending colon, terminal ileum, diaphragm, and peritoneum, but not in the lymph node. We recommended

genetic counseling to screen for a CRC syndrome related to genetic mutations. Gene sequencing identified a *MSH2* VUS (c.1168C>T (p.Leu390Phe)) (Fig. 2A). This VUS indicates that cytosine at position 1168 in the *MSH2* gene sequence is changed to thymine, and causing a missense substitution from leucine to phenylalanine at the 390th amino acid. *In silico* analysis showed that PolyPhen-2 (Polymorphism Phenotyping v2) [7] is benign, SIFT (Sorting Intolerant from Tolerant) [8] is tolerated, and Align GVGD (Grantham variation Grantham deviation) [9] is class C0, which suggests that the VUS has low pathogenicity.

After obtaining approval for the study, her children underwent genetic testing to screen for a hereditary syndrome. Among them, one son and daughter harbored the same *MSH2* mutation as the patient (Fig. 2B). It is important to note that PMP with the *MSH2* VUS was vertically transmitted. They were provided further counseling regarding the results, cancer risks related with *MSH2* mutations, and potential screening methods and prevention, including medical and surgical options.

Fig. 1. (A) Coronal view of the abdominopelvic-computed tomography shows a 9-cm cystic mass with internal multiple septations in the right to midline pelvis. (B, C) Left ovary (10 cm) and right ovary (5 cm) containing mucin with large amounts of mucinous ascites. (D) Histologic finding: hematoxylin and eosin staining of appendix (40×).

Fig. 2. (A) *MSH2* mutation analysis report. (B) Pedigree of the *MSH2* variant of unknown significance (VUS) mutation. VUS indicates a variant in a gene sequence that may be associated with clinical risk. Clinicians have difficulties managing VUS carriers and family members because there are no significant guidelines for VUS. In addition, most VUS carriers do not understand their genetic variants and may worry unnecessarily.

Discussion

To the best of our knowledge, this case demonstrates the first PMP case with a *MSH2* VUS mutation that was vertically transmitted between mother and children in Korea [1,2]. PMP is characterized by peritoneal cavity filling with mucinous ascites and epithelial mucin-secreting cells. The classification of PMP was controversial because its primary origin was unclear. However, a recent study on several cases showed that the primary origin of PMP is mainly colorectal sites (mostly appendix) [10]. PMP types are divided by pathologic definition into low- and high-grade by the World Health Organization [3]. The overall 5-year survival of patients with low-grade PMP is higher than that of patients with high-grade PMP (63% vs. 23%) [4]. The optimal treatment for PMP focuses on cytoreductive surgery followed by intravenous chemotherapy or hyperthermic intraperitoneal chemotherapy [5].

LS accounts for 1-3% of all CRC and is the most common inherited CRC syndrome. Among MMR genes, *MSH2* mutations account for the majority of LS cases [1,3,11]. The diagnostic approach for LS includes molecular testing, including immunohistochemistry, microsatellite instability, and germline sequencing of the MMR genes based on family history and determined by cost-effectiveness [6,7]. Our case involves a family with a *MSH2* mutation.

Gene mutation is defined as an alteration of the normal sequence of a gene that is associated with cancer risk or other clinic-pathological risks. The American College of Medical Genetics (ACMG) developed categories for VUS from Class I to V (not pathogenic to definitely pathogenic) [12]. According

to these classification guidelines, ACMG proposed further testing for VUS patients that is associated with each class of variants and composed of clinical testing and surveillance recommendations. Many geneticists make an effort to classify VUS in order to use the appropriate clinical approach. While genetic tests continue to improve and more genetic variants are found, there are few studies on the correlation between genetic variants and clinical pathogenicity.

Other tests proposed to aid in counseling VUS carriers include *in silico* analysis and family testing. The *in silico* method of computational analysis is based on protein multiple sequence alignments and expects pathogenic or neutral outcomes from missense substitutions. The predictive rate of *in silico* analysis ranges from 73% to 82% [13], but the analysis is not complete until the whole family is tested. This could cause the family members more anxiety and be expensive.

Although specific VUS guidelines have not yet been established, it is important that the surgeon should know the pathogenicity of VUS. Clinicians should be responsible for providing counseling to carriers, including a prediction of their risk and that of family members for developing the disease. In our case, the family members all agreed to undergo gene testing for the affected gene. They were all given proper screening and prophylactic choice according to gender and fertility status. Guidelines concerning cost-effective methods and the range of the screening population should be developed for the Korean population. This case report may affect future studies on the genetic risk of rare cancers such as PMP. Further large-scale, long-term studies to discover the pathogenicity of VUS are needed.

References

1. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large midwestern kindreds. Arch Intern Med 1966;117:206-12.
2. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell 1993;75:1027-38.
3. Papadopoulos N, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, et al. Mutation of a mutL homolog in hereditary colon cancer. 1994;263:1625-9.
4. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81:214-8.
5. Stoffel E, Mukherjee B, Raymond VM, Tayob N, Kastrinos F, Sparr J, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology 2009;137:1621-7.
6. Nummela P, Saarinen L, Thiel A, Järvinen P, Lehtonen R, Lepistö A, et al. Genomic profile of pseudomyxoma peritonei analyzed using next-generation sequencing and immunohistochemistry. Int J Cancer 2015;136:E282-9.
7. PolyPhen-2 (Polymorphism Phenotyping v2) program. [<http://genetics.bwh.harvard.edu/pph2/>]
8. Sorting Intolerant from Tolerant (SIFT) program. [<http://sift-dna.org>]
9. Align-GVGD program. [<http://agvgd.iarc.fr/>]
10. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol 2008;34:196-201.
11. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751-63.
12. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, et al; IARC Unclassified Genetic Variants Working Group. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 2008;29:1282-91.
13. Chan PA, Duraisamy S, Miller PJ, Newell JA, McBride C, Bond JP, et al. Interpreting missense variants: comparing computational methods in human disease genes CDKN2A, MLH1, MSH2, MECP2, and tyrosinase (TYR). Hum Mutat 2007;28:683-93.