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Case Report

Lynch Syndrome; A Tale of Two Cases Sharing The Same Destiny with Metachronous Tumor Development

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A B S T R A C T

Lynch syndrome (LS), is an autosomal dominant disease, accounts for approximately 1 to 2 percent of all colorectal cancers. Individuals with LS tend to develop cancers at a relatively young age and are at risk of multiple synchronous and metachronous malignancies. Several clinical criteria have been identified to assist in diagnosing LS. Subtotal or total colectomy is the procedure of choice for these patients as a result of high risk of multiplicity of lesions and metachronous tumors in time and colonoscopic surveillance is strictly recommended. Nevertheless, when the diagnosis of LS is neglected and the cancer is regarded as sporadic and treated accordingly, patients experience insufficient surgical interventions associated with metachronous malignancies, just like these two cases we report herein. The exact identification of the cases might decrease the number of misdiagnosis in this way and might decline the metachronous tumor development, with resulting in decreased morbidity, increased life quality, and improved survival. The article herein aimed to underline the importance of basic medical examination and colonoscopic surveillance that all of the clinicians dealing with cancer treatment should be aware of and the responsibility of surgical education centers on teaching the principles of cancer management to forthcoming surgeons during residancy.

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Olgu Sunumu

Lynch Sendromu; Metakron Tümör Gelişimi Nedeniyle Aynı Kaderi Paylaşan İki Olgunun Hikâyesi

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Ö Z E T

Lynch Sendromu (LS) otozomal dominant bir hastalık olup tüm kolorektal kanserlerin %1-2' sini oluşturmaktadır. LS'li bireyler göreceli olarak genç yaşta kanser gelişimine yatkındır ve multipl senkron ve metakron malignite gelişme riski altındalardır. LS tanısı koymaya yardımcı birkaç klinik kriter tanımlanmıştır. Multipl lezyonlar ve metakron tümörlerin zamanla yüksek risk olması nedeniyle bu hastalar için prosedür seçimi total ya da subtotal kolektomidir ve kolonoskopik takip şiddetle önerilmektedir. Fakat LS tanısı atlandığında ve kanser sporadik olarak addedilip buna göre tedavi edildiğinde, bu sunumdaki vakalarda olduğu gibi, hastalar metakron malignitelerle ilişkili olarak yetersiz cerrahi girişimleri deneyimlemektedirler. Vakaların kesin olarak tanımlanması; bu yolla yanlış tanıların sayısını azaltacak; azalmış mortalite, artmış hayat kalitesi ve geliştirilmiş hayat beklentisi ile sonuçlanacak olan metakron tümör gelişimini azaltacaktır. Bu makalede temel muayene ve kolonoskopik takibin öneminin kanser tedavisi ile ilgilenen tüm klinisyenlerin farkında olması; ayrıca ihtisas sürecindeki cerrahlara eğitim altındayken kanser yönetiminin prensiplerini öğreten cerrahi eğitim merkezlerinin sorumluluğunun öneminin altının çizilmesi hedeflemiştir.

1. Introduction

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome (LS), is an autosomal dominant disease caused by a germline mutation in a DNA mismatch repair (MMR) gene that accounts for approximately 1 to 2 percent of all colorectal cancers (1-3).

Individuals with HNPCC tend to develop cancers at a relatively young age (mean 45 years) and are at risk of multiple synchronous and metachronous malignancies (4). The probability of synchronous cancer is reported to be 18% whereas the risk of colon cancer development for operated patients in the following 10 years is determined to be 40% (5).

Several clinical criteria have been identified to assist in diagnosing LS. In 1991 The International Collaborative Group on HNPCC established the Amsterdam criteria to provide a definition of diagnosis and to require a careful assessment of the family history for cancer (6). Table 1 demonstrates the original Amsterdam criteria. A second version of these criteria was published in 1999 to provide more

relevance to the occurrence, in many families, of extracolonic tumors (Table 2) (4). According to the absence or presence of extracolonic malignancies, these families were divided into LS I (hereditary site-specific colorectal cancer) and LS II (colorectal cancer in association with extracolonic cancer) (7). Currently, revised Bethesta guidelines are more widely employed as a way to select those who are most likely to benefit from further genetic evaluation and serve as another tool to identify potential LS cases (Table 3) (8). Nevertheless, histopathology alone failed to identify all potential LS patients and lack of an adequate familial risk assessment might lead to misdiagnosis of LS when vague histopathology fails to trigger appropriate testing (9). From this point of view, surgeon should be attentive to the early onset of colon cancer, considering the probability of LS, and should interrogate Lynch family history and diagnose the case immediately with the abovementioned criterion. Subtotal or total colectomy is recommended to these patients as a result of high risk of multiplicity of lesions and metachronous tumors in time. In case of subtotal colectomy the risk of malignancy in the remaining colon segment should strictly be taken into consideration and periodical endoscopic follow-up and polyp excision should be recommended.

Table 1. Amsterdam Criteria I

• At least three relatives should have a diagnosis of colorectal cancer; • One of them should be first-degree relative of the other two; • At least one of the relatives should have colorectal cancer diagnosed at younger than aged 50 years; • At least two successive generations should be affected; • Familial polyposis should be excluded: • The diagnosis of cancer should be verified by clinical charts or death certificates.

Table 2. Amsterdam Criteria II

• At least three relatives should have a hereditary nonpolyposis colorectal cancer-associated neoplasm (colorectal, endometrial, ureter/renal, small bowel cancers); • All other criteria as Amsterdam I.

As the diagnosis of LS is neglected and due to the standard hemicolectomy as a surgical intervention with a diagnosis of sporadic colon carcinoma, patients might necessitate reoperation according to metachronous colonic tumors, leading to increased morbidity, decreased life quality and deteriorating survival, just like these two cases we report herein.

Case-1

A 43-years-old woman with a constipation complaint and medical history of standard right hemicolectomy in another center for right colon cancer 3 years ago, was admitted to our hospital for colonoscopic surveillance.

A malignant appearing ulcerovegetan mass anularly obstructing the lumen of the middle part of descending colon was determined in colonoscopy.

Table 3. Bethesda Criteria

• Colorectal cancer diagnosed in a patient aged <50 years; • Presence of synchronous or metachronous colorectal, or other Lynch syndrome-related tumors, regardless of age; • Colorectal cancer with microsatellite instability-H histology diagnosed in a patient aged <60 years; • Colorectal cancer or Lynch syndrome-related tumor diagnosed at aged <50 years in at least one first degree relative; • Colorectal cancer or Lynch syndrome-related tumor diagnosed at any age in two or more first-degree or second-degree relatives.

The histopathologic evaluation verified the biopsy specimen to be adenocarcinoma. The family history revealed that patient's older sister, father and paternal uncle had the diagnosis of colon cancer at ages 41, 52 and 48 years, respectively. Abdominal ultrasonography and computerized tomography demonstrated a constricting mass located in the middle of left colon and causing wall thickening of a segment with an approximately 4cm in size. Neither an increase in tumor markers, nor a distinct metastasis was detected. The other standard laboratory data were within normal ranges except a mild anemia (Hb:10.1g/dl.). The patient had the diagnosis of LS; metachronous colon carcinoma and a subtotal colectomy was performed. Histopathological examination was reported to be mild differentiated (signet cell) adenocarcinoma with a pathological grade of Astler-Coller B2 (Figure-1). The patient has been asymptomatic through 42 months of follow-up period after 5 episodes of chemotheraphy.

Case-2

A 54-year-old male admitted to our clinic was suffering from weight loss, weakness, constipation, and no defecation for a week. His previous medical history revealed that he had applied to another medical center 6 years ago with similar complaints and a standard left hemicolectomy was performed with the diagnosis of left colonic carcinoma. A palpabl right lumbal region mass with a size of approximately 15cm. was detected in physical examination.

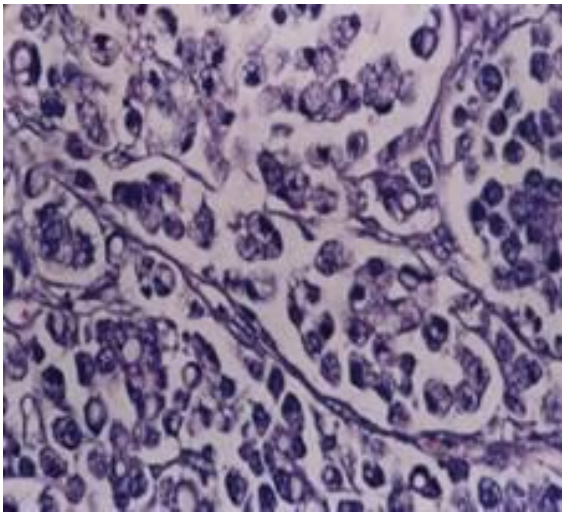

Figure 1. Histopathological examination was reported to be mild differentiated (signet cell) adenocarcinoma with a pathological grade of Astler-Coller B2.

Abdominal ultrasonography and computerized tomography revealed a mass lesion forming pseudokidney image and nearly obstructing a colon segment of 8 cm. in lenght. Multiple lympadenopathies in the adjacent colonic mesentery with a greatest diameter of 2 cm. was also recognised. Colonoscopic evaluation verified a vegetan mass lesion with malignant appearance, nearly obstructing colonic lumen. Histopathologic examination of the colonoscopic biopsy specimen was reported to be mild differentiated adenocarcinoma. Serum CA 19-9 level was found to be 3 times higher than normal. No distinct metastasis was detected. Patient's family history revealed that both of his brothers and father experienced colon cancer at the ages of 44, 51 and 56 years, respectively. With all these data patient was diagnosed to have LS of locally advanced metachronous colon carcinoma and a subtotal colectomy was performed. Histopathologically tumor was reported to be mild differentiated (signet ring cell) adenocarcinoma with a pathological grade of Astler- Coller C2. Patient received adjuvant chemotheraphy. Nevertheless he was lost due to disseminated hematogenous metastasis 4 years after the second operation.

2. Discussion

Individuals with a family history of colorectal cancer are at increased risk of developing colorectal cancer. In the past few decades an intense effort has been attributed to elucidate the genetic pathways playing a role in colonic carcinogenesis. Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (LS, HNPCC) are two of the most investigated samples of colorectal cancer due to inheritance. These syndromes are genetically and phenotypically well idenified pathologies with autosomal dominant inheritance, high penetrance and high colorectal cancer risk. However, these syndromes account for a little percentage in overall colorectal cancers. As a matter of fact, most of the colorectal cancers other than these syndromes achieve family history and familial risk. Although the exact reasons of familial risk have not been discovered yet, hereditary and environmental factors seem to be significantly effective.

Genetic factors are known to be independent risk factor for colorectal carcinogenesis for long years. LS is caused mainly by germline mutations in DNA mismatch repair genes, including MSH2, MLH1, MSH and PMS2 (10,11). Defects on this pathway lead to changes in the length of nucleotide repeat sequences of tumor DNA, termed as microsatellite instability. Microsatellite instability is a hallmark of the LS, occurring in more than 90% of tumors, whereas in sporadic colorectal cancer it is found in about 15% of cases. (12).

Colorectal tumors in people with the LS are usually proximal to the splenic flexure, often multiple, and associated with endometrial, breast, gastric, small intestine, hepatobiliary system, kidney, ureter, and ovarian cancer (13,14). Histological types of most of the cases are reported to be mucinous or signet ring cell adenocarcinoma and the prognosis are better than sporadic colon cancers. These patients do not possess multiple polyps, mostly having a few colonic adenoma. These adenomas are reported to be greater in diameter, developing at earlier ages than sporadic adenomas, showing more aggresive behaviour, and localizing more proximally (15). The LS was initially defined according to data based on family history. Features commonly associated with this syndrome include an autosomal dominant inheritance pattern with a high penetrance, early age

at diagnosis, tumors commonly affecting proximal colon, poorly differentiated histology with lymphocytic infiltration, and common presence of synchronous and metachronous colorectal cancer (16,17).

Individuals with a family history of colorectal cancer are at increased risk, and colonoscopic surveillance is strongly recommended. Colonoscopic surveillance is effective in reducing the risk of colorectal cancer in individuals with a strong family history, particularly, those who has a first degree relative with LS (18). Colonoscopic evaluation is appropriate for the first degree relatives of LS patients due to the predominance of proximally localized tumors. Screening colonoscopy is recommended annually begining at age 25 years or 10 years younger than the youngest age at diagnosis in the family (19). Colonoscopic screening at 3-year intervals is reported to decline the risk of colorectal cancer, preventing cancer deaths, and decreasing overall mortality by approximately 65% in Lynch families (19). The high incidence of colorectal cancers within 3 years of colonoscopy is reported to be an evidence that transformation from adenoma to carcinoma might be accelerated in LS (20). On the other hand, as a result of the diagnosis of advanced colorectal cancers with this screening prothocol, Lynch and some other authors recommend colonoscopy annually or at least in every 2 years (21). However opposing ideas questioning the usage of colonoscopy under the age of 50 also exist.. Colonoscopic surveillance with relatively shorter intervals has been proposed currently (18,22). Particularly, LS type-II patients and first degree relatives are suggested to undergo screening begining at age of 25 years old. Moreover, it is offered that females should be checked for pelvic examination, endometrial aspiration biopsy, and pelvic ultrasonography annually. Furthermore, some authors recommend prophylactic hysterectomy and bilateral salphingoopherectomy for postmenopausal women (21). Colonoscopic polypectomy has been reported to decline the incidence of colorectal cancer risk and to decrease both the incidence and mortality of cancer in individuals with family history of LS by providing early diagnosis (18).

Until recently, the Amsterdam criteria were the most important tool for the identification of LS. Nowadays, the revised Bethesda guidelines are more widely used. With the advances and refinements in molecular and genetic investigations, discussions are focussed on to select the families of which molecular genetic screening should be attempted. Nevertheless, one of the most important points is missed. That is, in many countries around the world, many physicians are not able to consult to specific laboratory or genetic tests according to economical difficulties or insufficient equipments. The only weapon to be used against colorectal cancer is clinical examination and colonoscopic evaluation. From this point of view, one of the major issues to be emphasized is to alert pyhsicians to suspect from LS in cases of early onset colorectal cancer with the family history. Clinical suspicion is of paramouth importance in the diagnosis of LS. Moreover, Ferreiara reported that to detect new cases of LS, family history is more important than microsatellite instability testing for adenomas of young patients (23). There is potentially a high risk of metachronous colorectal cancer if an initial cancer in a LS patient (defined according to Amsterdam criteria) is treated by partial colectomy. However, this risk can be lowered, either by performing a total colectomy at the time of initial surgery or possibly by effective postoperative surveillance (24). Both of our cases had 3 first degree relatives suffering from colon cancer and 2 successive generations were found to be effected. The earliest age of diagnosis was under 50 years in both families. Families of our patients completely comply with the definition of Lynch family according to Amsterdam criteria. As synchronous or metachronous tumor incidence is reported to be high in LS, prophylactic total colectomy and ileorectal anastomosis or hemicolectomy plus yearly colonoscopy is recommended to be the option of choice in various studies (25,26). However, both of the patients were considered to have sporadic colon carcinoma and accordingly underwent hemicolectomies, which is dramatically followed by metachronous tumor development without endoscopic surveillance and obliged patients to experience reoperation and led to death in one case. Second surgical intervention increases morbidity and worsens life quality. In the first case, 3 years and in the second, 6 years after initial surgical intervention metachronous tumor was detected and ıt was discovered that no screening prothocol was performed to these patients. Unfortunately, second case was diagnosed in an advanced stage and died of disseminated haematogenous metastasis after the second operation.

Our patients desperately experienced insufficient and inappropriate surgical intervention as a result of inattentive medical interrogation or physician's defecient knowledge about LS and misdiagnose it as sporadic colon cancer before they admitted to our clinic. Moreover, no screening prothocol was performed following their first

operation. According to us both of our patients share the same destiny as a result of misdiagnosis in their first operation and follow-up period. That is the reason why all of the surgeons should be very attentive in the diagnosis of sporadic colon cancer and to distinguish it from LS, particularly in case of early onset with family history. The medical education is a state of art and the major responsibility of a trainer is to educate his or her trainee such a way that provides efficient approach to the underlying etiologies, by means of knowledge and sensitive pover of judgement. We are all responsible to teach principles of cancer to forthcoming surgeons during residancy. All clinicians that are involved in the management of colorectal cancer patients should at least know the Amsterdam and Bethesda criteria in order to identify cases suspected of LS to establish appropriate surgical strategy. Being more aware of the criteria of LS might decrease the number of sacrifices in this way and might decline the metachronous tumor development. Systematic surveillance and individually designed treatment of affected patients might aid to determine malignancies at an earlier stage and subsequently improve the prognosis of the disease further.

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