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Short communication

Papillary thyroid carcinoma (PTC) in Lynch syndrome: Report of two cases and discussion on Lynch syndrome behaviour and genetics

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ABSTRACT

We present here two cases of papillary thyroid carcinoma (PTC) in patients affected by Lynch syndrome (LS). The first case is a 47-year-old woman with typical hereditary non-polyposis colorectal cancer (HNPCC) syndrome, reported with endometrial and ovarian carcinoma at age 43, and colon cancer at age 45. The patient underwent total thyroidectomy and central node dissection in 2007, at 47 years old, with a histological diagnosis of PTC (T1aN1a). Molecular genetics showed a germ-line mutation of the *MLH1* gene, 1858 G>T(E620X), with substitution of glycine with a stop codon at position 620. This mutation has pathogenetic significance and was considered responsible for the various tumours of the HNPCC spectrum. In particular, in the same kindred, spanning 5 generations, there were 5 members with colorectal cancer, 4 with endometrial cancer, 3 with gastric and 2 with breast cancer. The second case is a 34-year-old man with typical HNPCC syndrome with colonic resection for colon cancer at age 21. The patient underwent total thyroidectomy with central and lateral node dissection in 2010, at age 34, with a histological diagnosis of PTC with nodal metastases (pT4N1b). Molecular genetic analysis showed a germ-line mutation of the *MSH2* gene (thymine insertion at position 907). This mutation had pathogenetic significance and was considered responsible for HNPCC development. Two similar cases have been reported: a 39-year-old woman, and a 44-year-old woman, affected by HNPCC syndrome, with anaplastic thyroid carcinoma and undifferentiated thyroid carcinoma, respectively. We reviewed the Lynch syndrome literature on the history, genetics and expanding tumour spectrum of this condition.

1. Introduction

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder associated with germ-line mutation in one of the mismatch repair (MMR) genes, most commonly MLH1 and MSH2, and less frequently MSH6 and PMS2 [1].

HNPCC, also known as Lynch syndrome, is characterized by a strongly increased risk of developing colorectal cancer and several extracolonic malignancies, including carcinomas of the endometrium, ovary, ureter, stomach and small intestine [1,2]. Tumours develop at a relatively young age.

Recently, an increased occurrence of thyroid tumours has also been observed in kindreds with HNPCC, even if there are very few reports documenting that a germ-line mismatch repair mutation was basic for the occurrence of both colonic cancer and thyroid cancer. There were at least two reports, in which a precise germ-line mutation of the *MSH6* gene was considered responsible for the occurrence of both colonic and thyroid cancer: Stulp et al. in 2008 and Broaddus et al. in 2004 [1,3]. In particular, there was biallelic inactivation of this gene in the colonic cancerous tissue and in the thyroid tumoral tissue with mutation of the *MSH6* gene and a persistence of *MLH1*.

In this study, we report 2 patients with PTC associated with a typical HNPCC syndrome. We review the literature on history, genetics and unusual manifestations on inherited mismatch repair gene mutations.

1.1. History of HNPCC syndrome

In 1895, Aldred Scott Warthin, Chairman of the Department of Pathology at the University of Michigan in Ann Arbor, reported the first family with the disease we now call Lynch syndrome or

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HNPCC [2,4]. A woman who worked as his seamstress reported distress over the fact that many family members over several generations had succumbed to cancer and she feared the same for herself. Indeed she developed endometrial cancer, and died of that disease as she predicted [2,4]. Warthin studied her family in detail and published this large pedigree at 10 affected family members in 1913 outlining many generations affected by colonic, gastric, and uterine cancers [5,6]. Warthin concluded that there could be, at least in this instance, a familial predisposition to cancer. The family had emigrated from Germany to Michigan before the civil war; Warthin called them "Family G" [4–6].

Warthin performed an audit of 3600 cancer cases diagnosed in his laboratory between 1895 and 1912 and observed that approximately 15% of those had a positive family history of cancers of the gastrointestinal tract and uterus. Such cancers affected family members at a median age of 37.9 years and had a tendency for colorectal cancers (CRCs) to develop in the proximal colon. Warthin died in 1931 [4,5], and there was little consideration of this condition until the 1960s. Occasional case reports of this disease came from the Mayo Clinic in 1941 [7], England in 1956 [8] and a variety of locations in the 1960s [9–14].

In 1966, Henry Lynch described two families from Nebraska (N) and Michigan (M) that had similar cancer patterns involving multigenerations that were akin to the original Family G. He studied the data from over 650 Family G members and later published his "Cancer Family G Revisited" manuscript in 1971 that solidified the evidence which characterized this syndromic disease as having an autosomal dominant inheritance pattern and an early age of onset (average age at onset < 45 years) and involving adenocarcinomas of the colon, endometrium, and stomach [4,15]. A variety of hypotheses were proposed to explain the disease, but the time for discovery of the basis of hereditary cancer had not yet arrived. Lynch used the term "Cancer Family Syndrome" in his 1971 report [4,15].

In 1973, CR Boland, MD wrote a medical school thesis entitled "A familial Cancer Syndrome", recognizing the same disease; this led to the publication of 2 papers describing additional families with Lynch syndrome. In the first of these, the term "Cancer Family Syndrome" was used based upon Lynch's nomenclature [16]. However when a second family was reported later, it was noted that some families had a phenotype with only CRC, whereas other families had the characteristic non-colonic cancers we now recognize in this disease [4].

The terms Lynch syndrome I and II were used for the first time to distinguish those families with CRC only versus the full spectrum of cancers [17]. There is now evidence that at least some germ-line mutations can produce a CRC-predominant syndrome although the designations of Lynch syndrome I and II are no longer used or considered necessary. Interestingly, in 1985, Lynch first used the term "hereditary non-polyposis colorectal cancer" or HNPCC for this disease, which was the accepted term for many years [18–20].

In 1989, the International Collaborative Group on HNPCC (ICG-HNPCC) was established to develop the "Amsterdam criteria-I" for the diagnosis of HNPCC to facilitate identification of causative genes [21]. This was further expanded in 1999 to incorporate extracolonic tumours and was known as "Amsterdam criteria-II [22]. With the identification of several mutations within the MMR genes (MLH1, MSH2, MSH6, and PMS2), the National Cancer Institute held an international Workshop on Lynch Syndrome in Bethesda in November, 1997 [23].

They reported a standardized diagnostic panel of microsatellite markers and developed the Bethesda Guidelines for selecting patients' CRC for MSI analysis. [23,24]. These guidelines were revised and published HNPCC d in 2004 to include family history and specific pathologic features of CRC, such as signet ring cell features, Crohn's like reaction, mucinous features and location of the tumour in the right colon [25].

In 2008, Hampel et al. demonstrated the feasibility of large-scale immunohistochemistry (IHC) that could aid in directing genetic testing [26]. In 2009, the Jerusalem Workshop recommended routine MSI testing or immunohistochemistry for all CRCs diagnosed in patients below the age of 70 years [27].

These recommendations were incorporated into the Evaluation of Genomic Application in Practice and Prevention (EGAPP) evidence report [28].

1.2. Genetics of HNPCC syndrome

The majority of colorectal cancers (CRC) develop sporadically from somatic alterations in colon epithelial cells; however in up to 30% of cases, CRC develops in patients that have a strong family history [2].

Patients with affected first-degree relatives have a 2–10 times increased risk of developing CRC and in the absence of a Lynch or polyposis syndrome probably harbour incompletely penetrant variants in a range of genes [2].

Lynch syndrome, also known as HNPCC, is an autosomal dominant disorder associated with a germ-line mutation in one of the DNA mismatch repair (MMR) genes. The normal function of the MMR proteins is to proofread the nucleotide sequence for potential base-base errors that occur during DNA synthesis. Microsatellites are short repetitive sequences that are distributed throughout the human genome.

Defective MMR causes variations within the micro satellites, manifesting as a gain or loss in repeat length. This is described as microsatellite instability (MSI) [29–32]. Cancers that possess more than 40% microsatellite variations are described as high frequency MSI (MSI-H). Interestingly, this phenotype is also observed in 15% of sporadic CRCs due to somatic methylation of the MLH1 promoter region. Further genotyping for the BRAF somatic V600E mutation can be performed to confirm somatic occurrences of MSI. Mutations of the BRAF with methylation of MLH1 are typical of sporadic CRC and are almost never seen in Lynch syndrome [33–35]. Tumors that have no MSI are microsatellite stable (MSS) and those that possess less than 40% microsatellites variations are low frequency (MSI-L), although the relevance of this group is uncertain and these tumours are not considered microsatellite unstable [33–35].

The majority of individuals with Lynch syndrome possess at least one pathogenic germ-line mutation of the MMR genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, *MLH1* and *MSH2* genes are by far the most commonly mutated in Lynch syndrome patients accounting for 70% of the mutations identified (32% in MLH1 and 38% in MSH2) [36,37]. Individuals who carry mutations in the *MSH2* gene have preponderance for developing extracolonic cancer and a lower frequency of CRC when compared with MLH1 [38,39].

MSH6 mutations are commonly linked with gastrointestinal and endometrial cancer, and a later age of presentation [40,41]. MSH6 is also recognized as a frequent cause of atypical Lynch syndrome [40,41]. Senter et al. analysed 99 probands diagnosed with Lynch syndrome associated tumors showing isolated loss of PMS2 and demonstrated germ-line PMS2 mutation in 62% of probands [42]. Among families with monoallelic PMS2 mutations, 65.5% met revised Bethesda guidelines and the penetrance for monoallelic mutation carriers was lower than for the other MMR genes [42].

Recently, constitutional 3′ deletions of EPCAM-expressing tissues resulted in tissue-specific MSH2 deficiency [43]. Kempers et al. performed a cohort study comparing 194 patients carrying the EPCAM deletion to 473 patients carrying a mutation in MLH1, MSH2, MSH6, or a combined EPCAM-MSH2 deletion. Carriers of an