Biomedicine & Pharmacotherapy 74 (2015) 9–16

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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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ARTICLE INFO

Article history:
Received 22 May 2015
Accepted 23 June 2015

Keywords:
Papillary thyroid carcinoma
Lynch syndrome
Clinical and genetic characteristics

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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http://dx.doi.org/10.1016/j.biopha.2015.06.008
0753-3322/

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

EPCAM deletion had a 75% cumulative risk of colorectal cancer before the age of 70 years, which did not differ significantly from that of carriers of combined EPCAM-MSH2 deletion or mutations in MSH2, but was higher than noted for carriers of MSH6 mutation. Only those with deletions extending close to the MSH2 promoter had an increase risk of endometrial cancer. Therefore, these results underscore the effect of mosaic MSH2 deficiency leading to variable cancer risks and could form the basis of an optimized protocol for the recognition and targeted prevention of cancer in EPCAM deletion carriers [44].

So far, genome wide association studies have identified approximately 20 gene variants associated with the development of sporadic CRC [45]. Wijnen et al. have identified the single nucleotide polymorphism rs16892766 (8q23.3) and rs3802842 (11q23.1) be significantly associated with CRC risk in Lynch syndrome families [46]. For rs16892766, possession of the C-allele was associated with an elevated risk of CRC in a dose-dependent fashion, with homozygosity for cc being associated with 2.16-fold increased risk. For rs3802842, the increased risk of CRC associated with the C-allele was only found among female carriers, while CRC risk was substantially higher among homozygous compared to the heterozygous carriers of the C-allele. In an additive model of both variants, the risk was significantly associated with the number of risk alleles. The effects were stronger in female carriers than in male carriers. Such modifiers may aid in identifying high-risk individuals who require more intensive surveillance [46].

Interestingly, of all the families who meet the Amsterdam-1 criteria, approximately 80% of families carry a hereditary abnormality in a MMR gene. Lindor et al. identified 161 Amsterdam-1 pedigrees and compared families with and without MMR abnormalities [47].

Families who fulfilled the Amsterdam criteria-1 and did not possess a DNA MMR defect did not share the same cancer incidence as families with hereditary MMR deficiency. Relatives in such families carried a modest risk of developing CRC at an older age without extracolonic malignancies when compared to those who have an identifiable mismatch repair gene defects. Therefore, in order to distinguish these cohorts apart, the designation of "familial CRC type X" was suggested for this type of familial aggregation of CRC [47].

The Human Variome Project has recently established a pilot project in conjunction with the International Society for Gastrointestinal Hereditary Tumours in order to interrogate all inherited variation affecting colon cancer susceptibility genes [48]. Genotypic-phenotyping data are stored in the InSiGHT Colon Cancer Gene Variant Databases [49].

This registry provides a deeper understanding into both rare and common forms of hereditary CRC syndromes [49]. Recently, InSiGHT formed an international panel of researchers and clinicians to review MMR genes variants submitted to the database in an effort to develop, test and apply a five-tiered scheme to classify 2360 unique constitutional MMR gene variants [50].

Out of the 12,006 variant and 2091 variants as Class 1 entries in the InSiGHT database, the final outcome of standardized five-tiered InSiGHT classification of constitutional *MMR* gene variants included 2641 variants as Class 5 (pathogenic), 239 as Class 4 (probably pathogenic), 6982 as Class 3 (unknown), classification as Class 2 (probably no pathogenicity) and 2091 as Class 1 (no known pathogenicity). This is the first large-scale comprehensive classification effort undertaken for the curation of locus specific database (LSDB) and providing summary information to assign variant pathogenicity [48–50].

1.3. HNPCC sndrome expanding tumour spectrum

Malignancies most frequently associated with HNPCC are localized in colon and rectum, endometrium, ovary, small intestine, stomach, ureter and renal pelvis [1,21,22]. Less frequent manifestations include non-Hodgkin lymphoma, rhabdomyosarcoma, breast carcinoma, fibrous histiocytoma, adrenal cortical carcinoma, thyroid carcinoma (anaplastic/undifferentiated), pancreatic medullary carcinoma, prostate adenocarcinoma, liposarcoma, hepatic cholangiocarcinoma, uterine carcinosarcoma, renal cell carcinoma (clear cells), brain tumours (Turcot syndrome in the variant associated with HNPCC facilitating the occurrence of glioma, astrocytoma/glioblastoma), and sebaceous glands carcinoma [1,50–52].

In the past, the Lynch syndrome tumour spectrum has primarily been defined through an epidemiological and statistical approach. From a clinical point of view, this approach is of course still very valid as many clinicians will be primarily interested in tumours that have a significantly increased risk of developing in their patients. Cumulative cancer risks for Lynch syndrome were usually based on retrospective cohort analysis of families meeting the Amsterdam criteria, often including families without proven mutations and untested first-degree relatives. More recently studies have focused on proven mutation carriers only. Interestingly, the risk for gastric, ovarian, ureter/renal pelvis and brain tumours appears to be higher for carriers of MSH2 mutations than for carriers of MLH1 mutations [1,38,47,50–52]. Again, patients with atypical Lynch syndrome tumours more often have been reported to carry an MSH2 rather than an MLH1 mutation [1].

2. Case reports

2.1. First case

The first case we reported is a 47-year-old female, affected by Lynch syndrome, with prior hysteron-adnexectomy for uterine adenocarcinoma (G1pT1bpN0) and right ovarian adenocarcinoma (G2pT1a pN0) in February 2007 and total colectomy for colon cancer (pT1N0M0) in December 2009 (Figs. 1–3).

Thyroid ultrasound performed in November 2010 as a part of the follow-up program showed a 6 mm right lobe nodule. ^{18}F-FDG PET-TC confirmed a hyperactive thyroid nodule and FNA biopsy documented PTC. In May 2007, the patient underwent total thyroidectomy with central node dissection. At histology, the PTC had a maximum diameter of 6 mm, with no infiltration of the glandular capsule, metastases were present in 5 of 14 resected lymph nodes (pT1a, N1a, Stage III) (Fig. 4). The patient underwent radioiodine remnant ablation with 100 mCi following recombinant human thyroid stimulating hormone (rh-TSH) and at 7 years follow-up, neck ultrasound is negative, thyroglobulin (Tg) is < 0.1 ng/mL, and Tg-Antibodies (Tg-Ab) are negative.

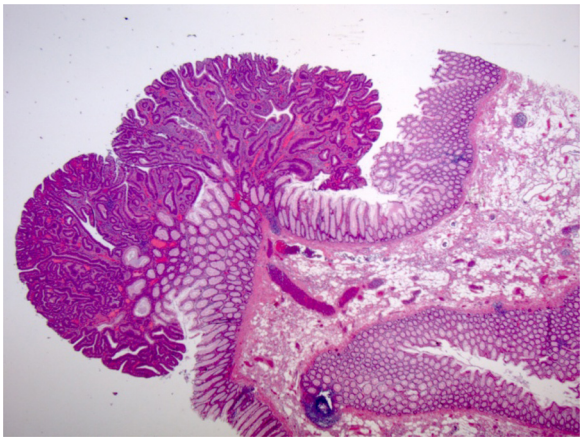

Fig. 1. First case. Adenocarcinoma of the colon with polypoid growth and invasiveness limited to the submucosa. Magnification 5 ×, hematoxylin and eosin.

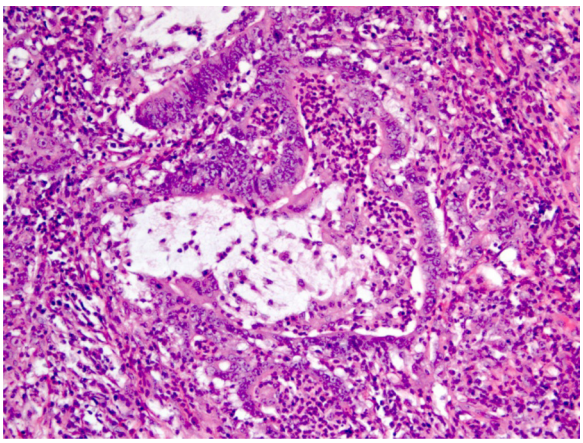

Fig. 2. First case. Low-grade adenocarcinoma of the colon with intraluminal necrosis. Magnification 20 ×, hematoxylin and eosin.

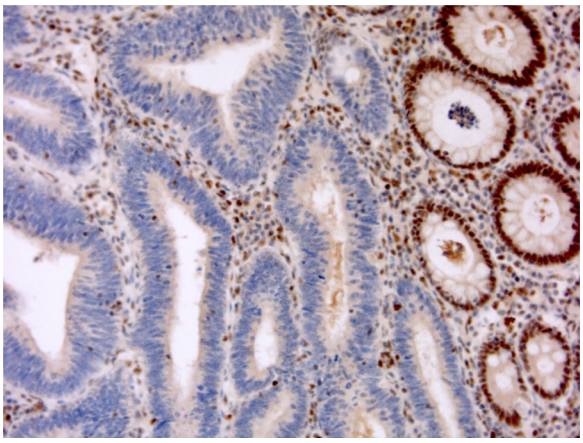

Fig. 3. First case. Immunostaining of adenocarcinoma of the colon for mlh1. Strong nuclear staining of non-neoplastic gland cells compared with the loss of nuclear positivity of the cancer cells. Magnification 20 ×.

The patient is a member of large HNPCC kindred spanning 5 generations. The pedigree is demonstrated in Fig. 5. There were at least 5 members with colorectal cancer, 4 with endometrial cancer, 3 with gastric and 2 with breast cancer.

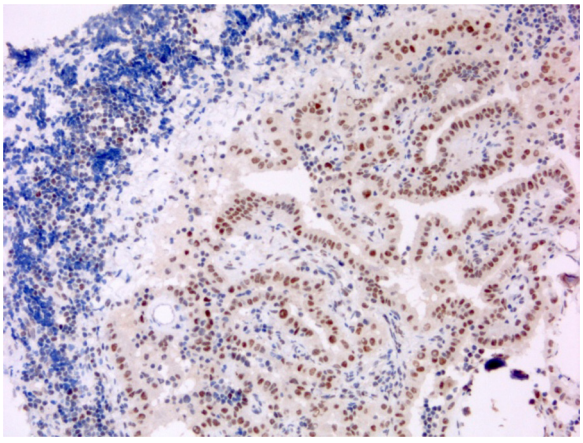

Fig. 4. First case. Lymph node metastases of PTC. Immunostaining for TTF identifies metastatic cells of PTC in a limph node. Magnification 10 ×.

Molecular genetics analysis showed a germ-line mutation of the *MLH1* gene, 1858 G>T(E620X), determining substitution of glycine with a stop codon at position 620. This mutation has pathogenetic significance and was considered responsible for HNPCC development.

Two additional heterozygosis variants of *MLH1* (IVS11-8T>A and IVS13+14G>4) and one variant of *MSH2* gene (IVS1+9C>G) were also identified. This variant should not have a causative role. The patient is presently alive and well 5 years after hysteron-adnexectomy, 3 years after colectomy and 9 months after thyroid-ectomy.

2.1.1. Methods

2.1.1.1. MSI analysis. All tumours of the patient were analyzed for microsatellite instability. Standard MSI analysis was performed on paired tumour normal tissue DNA samples using the National Cancer Institute (NCI) panel of microsatellite markers plus an additional panel of mononucleotide markers as recommended and described previously [53,54]. Tumours were scored as MSI-H (high microsatellite instability), according to the international guide-lines [50–54].

2.1.1.2. IHC assay. Conventional IHC for MLH1, MSH2, MSH6, PMS2 proteins was performed on all three tumours of the patients

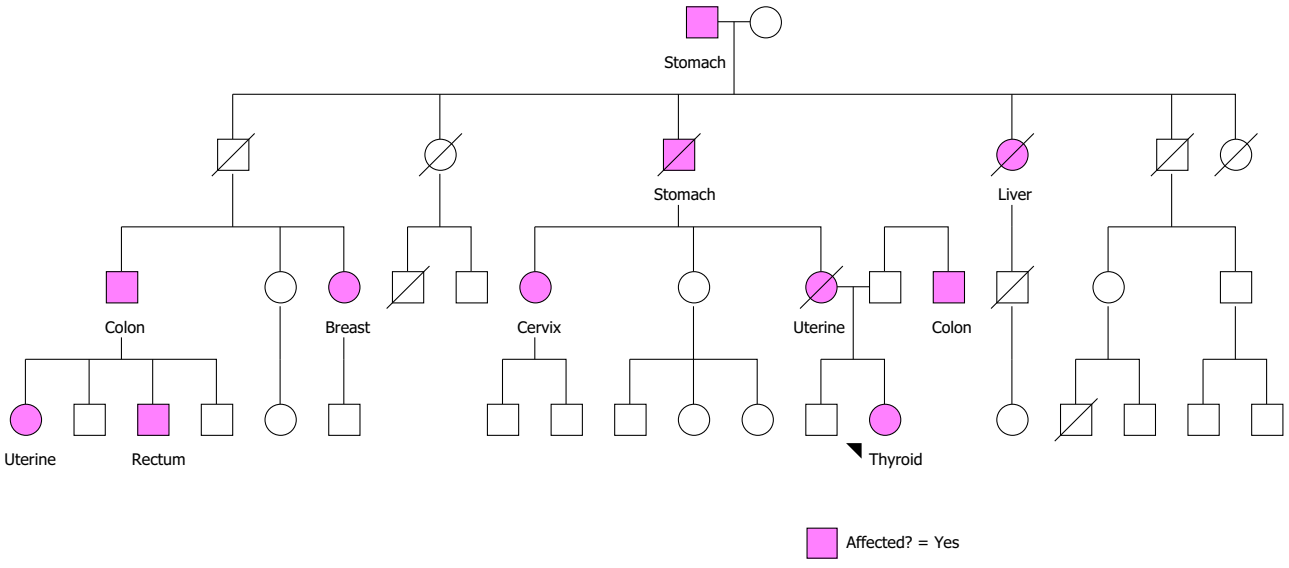

Fig. 5. Four generation pedigree of the proband; coloured symbols indicate individuals affected by cancer.

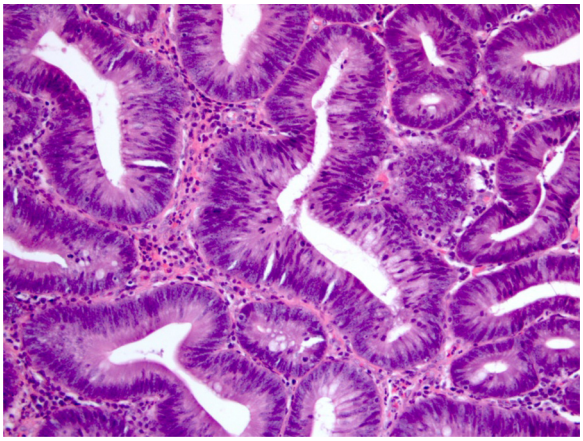

Fig. 6. Second case. Colon cancer. Moderately-differentiated adenocarcinoma of the colon with glandular architecture, nuclear atypia and cellular overlapping. Magnification 20 ×, hematoxylin and eosin.

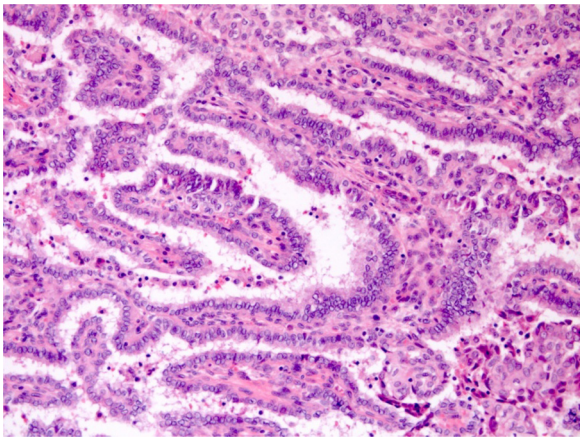

Fig. 7. Second case. PTC: the tumor shows the typical papillary architecture with well-developed fibrovascular cores and branching. Magnification 20 ×, hematoxylin and eosin.

as previously described [55]. A case was considered negative for protein expression only when there was a complete absence of nuclear staining of neoplastic cells in the presence of an unquestionable internal positive control in non-neoplastic cells.

2.1.1.3. DNA mismatch repair (MMR) genes analyses. After genetic counselling and informed consent, MMR germ-line mutation analyses were carried out by bidirectional sequencing on an automatic ABI3100 DNA analyzer (Applera). Point mutations of gene were searched by PCRs of genomic DNA with exon-specific primer pairs and bidirectional sequencing. Multiplex Legation-dependent Probe Amplification (MLPA) was utilized to identify large gene deletion.

2.2. Second case

The second case we reported is a 34-year-old male, born in Buenos Aires, Argentina. The patient underwent transverse colon resection in 1997, at 21 years old, because of colon cancer (Fig. 6).

In April 2010, the patient presented a left lateral neck enlargement. Ultrasound and CT of the neck confirmed the presence of a 10 × 13 mm thyroid nodule, suggestive for malignancy with enlargement of multiple nodes in the left lateral neck (maximum size 38 mm). FNA biopsy documented a PTC (10 × 13 mm) in the thyroid left lobe, and malignant epithelial cells with malignant architecture, suggestive for thyroid origin in the lateral lymph nodes, which also showed psammoma-liked calcifications.

The patient underwent total thyroidectomy with central and lateral neck node dissection. Histological examination showed a typical PTC with low-grade chronic peritumoral inflammation and no angiolymphatic invasion. Twenty-one of 27 lymph nodes were metastatic, in particular, in 5 of them, tumour infiltration extended beyond the lymph nodal capsule (stage pT4pN1b) (Figs. 7–9). The patient underwent radioiodine therapy with 150 mCi of radioiodine after thyroid hormone withdrawal and at follow-up (4 years) the neck ultrasound is negative, Tg is < 0.2 ng/mL, Tg-Ab was negative.

The family tree is reported in Fig. 10, showing familiarity for colon cancer (at least 4 affected members in three generations), suggestive for Lynch syndrome type I (endometrial carcinoma was also present in one affected female member). Neither APC

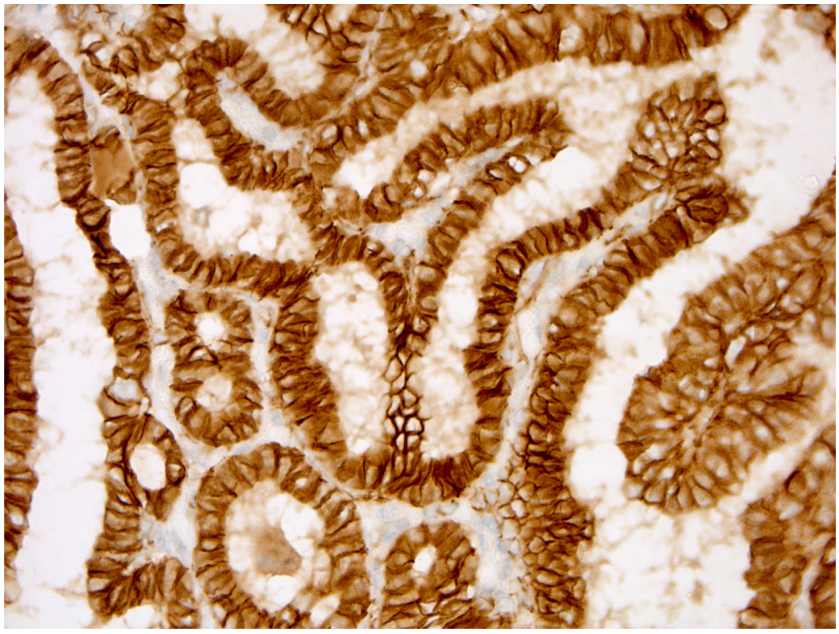

Fig. 8. Second case. Immunostaining of PTC for β-catenin. Diffuse and strong membrane staining of tumor cells. Magnification 40 ×.

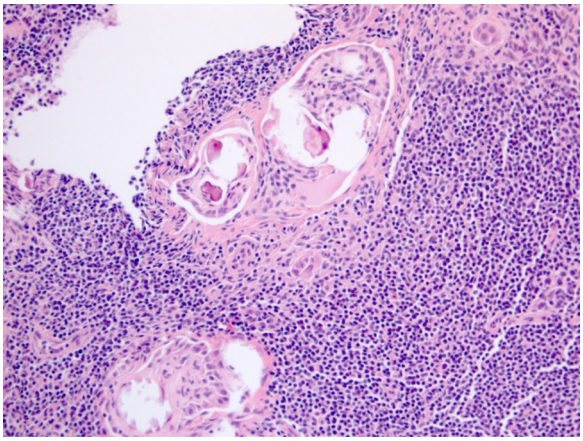

Fig. 9. Second case. Lymph node metastases. Metastatic cells of PTC and psammomatous bodies in a lymph node. Magnification 20 ×, hematoxylin and eosin.

mutations nor mutations in *MMR* genes have been detected in this patient or in other kindred members up to now.

2.2.1. Methods

2.2.1.1. IHC assay. Conventional IHC for MLH1, MSH2, MSH6, PMS2 proteins was performed on all tumours in three of the patients as previously described [56]. A case was considered negative for protein expression only when there was a complete absence of nuclear staining of neoplastic cells in the presence of an unquestionable internal positive control in non-neoplastic cells.

2.2.1.2. DNA mismatch repair (MMR) genes analyses. After genetic counselling and informed consent, MMR germ-line mutation analyses were carried out by bidirectional sequencing on an automatic ABI3100 DNA analyzer (Applera). Point mutations of gene were searched by PCRs of genomic DNA with exon-specific primer pairs and bidirectional sequencing. Multiplex Legation-dependent Probe Amplification (MLPA) was utilized to identify large gene deletion.

3. Discussion

Lynch syndrome, also known as HNPCC, is an autosomal dominant disorder with a germ-line mutation in one of the DNA MMR genes and is characterized by a strongly increased risk of developing colorectal cancer and several extracolonic malignancies, including carcinoma of the endometrium, ovary, ureter, stomach, and small intestine [1,2].

Traditionally, thyroid cancer is not considered to be part of the Lynch syndrome tumour spectrum. Recent report however reported such an association in at least two patients belonging to a Lynch syndrome with documented germ-line mutation of a *MMR* gene. These findings suggested that the thyroid tumour was not incidental, but likely developed in association with the underlying germ-line defect, which involved in both cases the *MSH2* gene.

In particular, 2 cases have been previously reported [1,51]. The first case is a 39-year-old woman, affected by an anaplastic carcinoma of the thyroid. At the time of thyroid surgery, there were two lung nodules and a possible pancreatic metastasis. The patient died approximately seven months after the initial diagnosis. The family history was significant for endometrial cancer in the mother

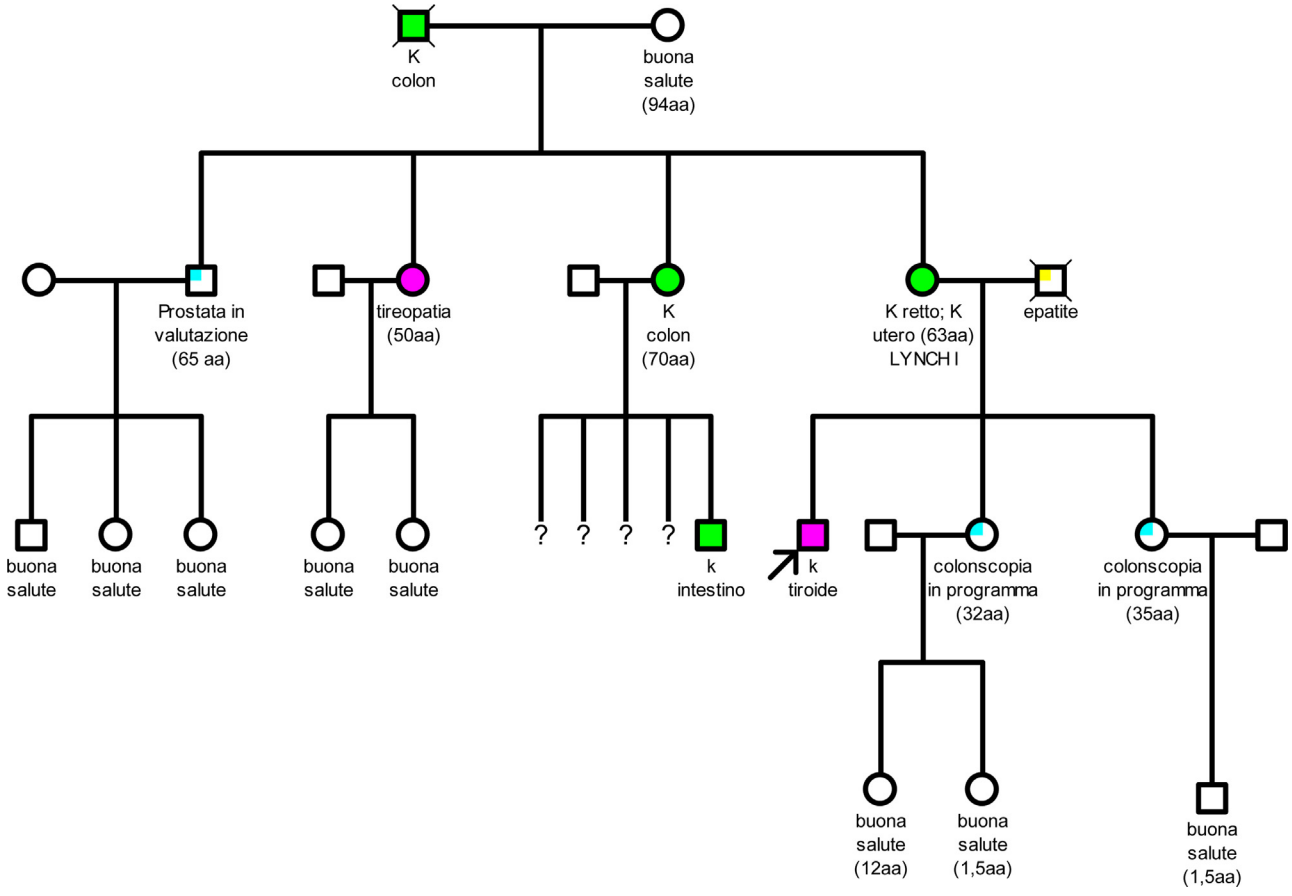

Fig. 10. Second case: the family tree.

(age 48) and one niece (age 38), and for endometrial cancer (age 43) plus colon cancer (age 58) in a sister, and another colon cancer in a nice (age 37) and endometrial cancer (age 41). The niece with both colon cancer and endometrial cancer underwent *MLH1* and *MSH2* full sequence analysis and was found to have a deleterious mutation of *MSH2* (mutation Q824X, resulting premature truncation of the MSH2 protein at AA824) [51].

The second reported case was a 44-year-old woman with a recent history of colorectal adenoma and an undifferentiated carcinoma of the thyroid. Genetic analysis of the *MSH2* gene in this patient revealed the c1704-1705 del AG mutation, already known to segregate in her family. Her undifferentiated thyroid carcinoma showed completed loss of immune-histochemical expression of the MSH2 and MSH6 protein, in the presence of normal positive internal controls and no loss of the MLH1 and PMS2 protein. Of the 5 microsatellite markers tested, BAT26 showed instability. Therefore, the thyroid tumour was classified as MSI-low [1].

Undifferentiated thyroid carcinoma is not commonly associated with Lynch syndrome. However, in both these cases, there was immunohistochemical loss of expression for the MSH2 and MSH6 protein, suggesting that this tumour was linked to the underlying mutation in the *MSH2* gene.

Loss of MSH6 expression in tumours is often observed in case of germ-line *MSH2* mutations and can be explained by loss of its stabilizing partner *MSH2*. Broaddus et al. contended that for both an adrenal and a thyroid carcinoma, a *MSH2* mutation was causally linked, because the tumour showed loss of MSH2 protein with immunohistochemical staining, but retained expression of MLH1 [51].

In the past, the Lynch syndrome tumour spectrum has primarily been defined through an epidemiological and statistical approach. After initial clinical diagnosis mainly based on classical Amsterdam criteria, more recent studies have focused on proven mutation carriers only. Comparative studies have shown that the risk for gastric, ovarian, ureter/renal pelvic and brain tumours appears to be higher for carriers of *MSH2* mutation than for carriers of *MLH1* mutations [1].

Our first case report described a HNPCC kindred member with the unique concomitant colon cancer, endometrium and ovary cancer, and thyroid carcinoma. In fact, in the patient described by Stulp et al., there was only a concomitant colorectal adenoma, and in the patient described by Broaddus et al., belonging to a typical Lynch syndrome with known germ-line mutation, thyroid cancer was the only tumour, rapidly determining the death of the patient [1,51]. Our patient had a similar age, but she differed in two features:

- her germ-line mutation involved *MLH1* gene instead of *MSH2*;
- because of intensive screening due to the two previous malignancies, her thyroid tumour was diagnosed very early at 6 mm of diameter, with no capsule invasion.

Histotype was typical PTC with lymphocytic thyroiditis and, despite early metastatic spread to cervical lymph nodes (5 of 14 had metastases). It is likely that her PTC will have a better prognosis than her two other tumours. For the moment, speculation concerning possible pathogenesis is premature. Certainly thyroid cancer may occur in patients with *MLH1* and not only in patients with *MSH2* germ-line mutations.

Our second case report shows some similarities with previous reports, namely concerning the *MMR* gene with the germ-line mutation, which is similar, i.e. *MSH2*, but with some differences. Differences include:

- male gender is unusual in thyroid cancers associated with colorectal cancer within familial amyloid polyneuropathy (FAP) kindreds;
- the very young age for the occurrence of colonic cancer, that is more similar to typical FAP associated than to HNPCC associated colon cancer;
- the aggressive biological behaviour of all three thyroid cancers associated with HNPCC, which is opposite to the usual indolent behaviour of FAP associated PTC.

Even if the number of thyroid cancers occurring in HNPCC kindreds is relatively low, it is probably greater than the 2 reported up to now. Both of these 2 patients had a germ-line *MSH2* mutation. Numbers are too small to draw any conclusions concerning genotype–phenotype correlation, in the sense that this peculiar *MMR* gene could predispose specifically to thyroid cancer. It is likely that future HNPCC patients could have thyroid cancer in association with germ-line mutations in other *MMR* genes.

Concerning most frequent manifestations of HNPCC, there have been some attempts at correlating tumours in some organs with germ-line mutations in peculiar *MMR* genes. According to Stulp et al., the risk for gastric, ovarian, ureter-renal pelvis and brain tumours appears to be higher for carriers of *MSH2* mutations than for carriers of *MLH1* mutations, whereas *MLH1* carriers show a greater incidence of small intestine tumours [52–54].

Two other comments can be made. First of all, HNPCC associated thyroid cancers are usually not typically papillary, but more often undifferentiated or anaplastic, with a worse prognosis, and affect both females and males whereas FAP associated thyroid carcinomas are almost always PTC (frequently showing the so called cribriform-morular variant) and affect quite exclusively the female gender (F:M ratio = 80:1 in a recent review of literature cases since year 1999) [55–57]. Moreover, both HNPCC and FAP could be associated in a minority of cases with brain tumours (Turcot syndrome) and thyroid cancer. Interestingly, there is a different gender preponderance and type of tumours between the two syndromes. FAP is mostly associated with medulloblastomas and PTC, with better prognosis, usually in females, whereas HNPCC is mainly associated with gliomas or glioblastomas, or with undifferentiated thyroid tumours, with less female preponderance [57,58].

If comprehensively screened, thyroid cancer will probably be found in a greater number of members of HNCCP kindreds. Intensive screening seems justifiable, because of the aggressive biological behaviour of these thyroid tumours. In fact, within the frameshift of colon cancer – thyroid cancer syndromes, whereas the FAP associated thyroid cancer has an invariably good prognosis, which discouraged systematic intensive screening for it in affected members, HNPCC associated thyroid cancer seems to be more aggressive and deserving of a more proactive diagnostic approach.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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