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Muir-Torre Syndrome: a Long Way to Diagnosis

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Abstract

Muir-Torre syndrome, a subtype of Lynch syndrome, is a rare genetic disorder. We present the case of a female patient with a long family and personal history who was diagnosed with numerous benign and malignant tumours of various histology, including some with sebaceous features, beginning at the age of 41. The majority were cutaneous tumours, treated with complete resection, but they frequently recurred. Visceral cancers included endocervical adenocarcinoma, vulvar squamous-cell carcinoma and urothelial carcinoma, treated surgically, followed by systemic oncological treatments and external beam radiotherapy.

Following a 20-year evolution, extensive genetic blood testing revealed a pathogenic variant in the MSH2 gene, c.1861C>T (p.Arg621*), in heterozygous state. In light of this unusual clinical presentation and molecular profile, the patient was finally diagnosed with Muir-Torre syndrome. The prognosis was poor, with an inoperable recurrence of the urothelial carcinoma and extensive lymph node dissemination of a vulvar squamous cell carcinoma.

Keywords: *Lynch syndrome; Muir-Torre syndrome; Genetic disease; Deficient Mismatch Repair*

Case Reports

1. Introduction

Muir Torre syndrome (MTS) is a rare genetic disease, considered a subtype of hereditary non-polyposis colorectal cancer (HNPCC), also called Lynch syndrome, an autosomal dominant disorder with variable penetrance (1–4). The concerned genes (MSH2, MSH6, MLH1, MLH3, PMS2) are involved in DNA repair mechanisms (Mismatch Repair/ MMR) and their pathogenic variants lead to microsatellite instability (MSI)(5–7). Clinically, this pathology is characterized by the presence of multiple visceral and skin tumours, both malignant and benign, with the typical occurrence of cutaneous sebaceous tumours. The clinical diagnostic criteria include the presence of at least one visceral cancer in a patient under the age of 60, with positive personal and family history of cancer, and the

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presence of at least one sebaceous tumour. Another distinctive feature is the appearance of skin tumours, especially on the face and scalp, preceding the visceral ones.

So far, approximately 200 such cases have been published in the literature. Table 1 summarises the main diagnostic criteria for Muir-Torre syndrome (8).

Table 1. Muir-Torre Syndrome- diagnostic criteria

Muir-Torre Syndrome – Diagnostic criteria
Minimum 1 sebaceous tumor • Adenoma • Epithelioma • Carcinoma • Basal cell carcinoma with sebaceous features
Minimum 1 visceral malignant tumor
Age <60 years (disease onset/first tumor)
Positive family history
Positive personal history • Lynch Syndrome- related malignancies

2. Case Presentation

Clinical features and patient history

We present the case of a female patient with a significant family history of cancer, as following: father with colorectal cancer, deceased at the age of 50, one sister with breast cancer and another sister with gastric cancer, and four other relatives diagnosed with different types of cancer, mostly of breast or gynecological origin, all at young ages, the youngest being diagnosed at 20 years of age. Figure 1 shows this family's cancer history genealogical scheme.

The first symptom occurred at the age of 41, when she presented with a nasal tumour located in the left alar region, which was completely surgically removed and diagnosed as a superinfected keratoacanthoma. She returned 6 years later (age 47) with an endocervical tumour, diagnosed as stage IB1 papillary serous endocervical adenocarcinoma. A total hysterectomy with bilateral salpingo-oopherectomy was performed, followed by local pelvic radiotherapy with a dose of 50Gy in 25 fractions. Periodic checks were carried out for 5 years, the patient being disease free.

At the age of 53, the patient returned with multiple small tumours at the left alar and cervico-occipital level, which, after excision, were diagnosed as basal cell carcinomas. In the next two years she presented with multiple and various skin tumours, mostly perioral and palmar, pathologically diagnosed as grade 1 keratinized squamous cell carcinoma), all staged at the time of excision as stage I (pT1N0). The patient returned with multiple tumours of the scalp, which turned out to be sebaceous adenomas and carcinomas. Additionally, she presented multiple other skin tumours of various histological subtypes: G1 keratinized squamous cell vulvar carcinoma, (excised pT1b L0V0R0), benign fibrous axillar histiocytoma (excised), submental dermatofibroma (excised, pT1), G1 keratinized squamous cell carcinoma at the palmar level (excised pT1).

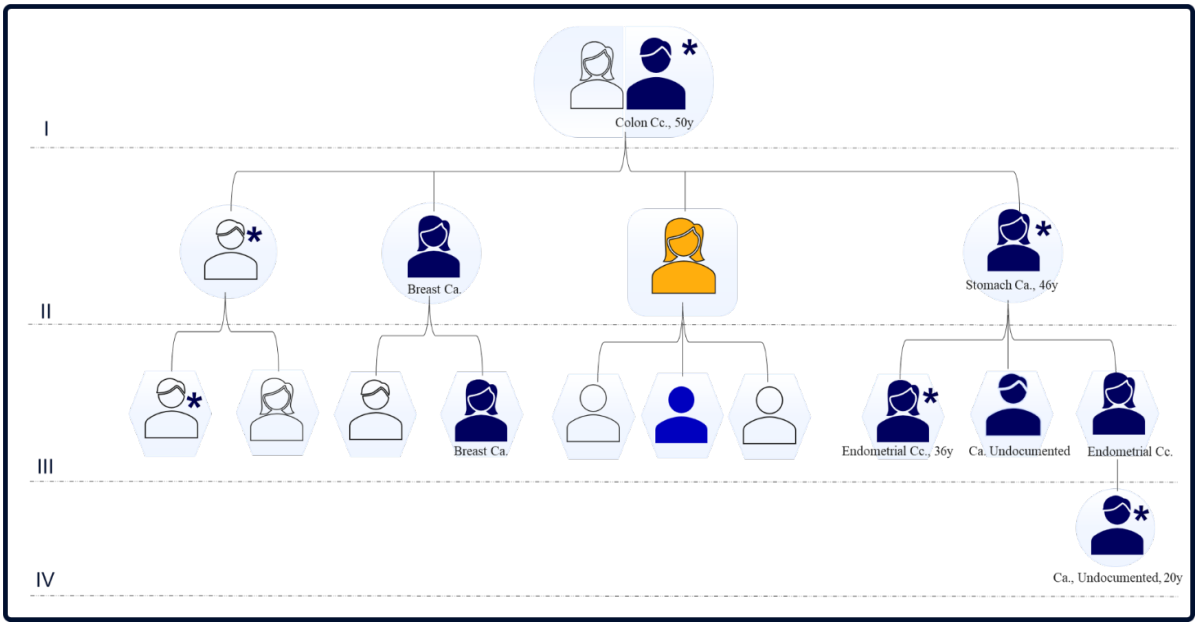

Figure 1. Family tree and cancer history: dark blue= cancer present; yellow= presented patient; blue= mutation identified by genetic testing; *= deceased; y= years-old; CC= carcinoma, Ca=cancer

In the upcoming period, the skin lesions progressed, with repeated presentations for the excision of tumours from the face, anterior thorax and hand. The following histological types were identified: actinic/seborrheic keratosis, squamous carcinoma keratinized G2, molluscum contagiosum and sebaceoma. Throughout this time, the patient did not exhibit any systemic symptoms and there was no alteration of the general condition or quality of life.

At the age of 62, she experienced mild dysuria. Following a computed tomography (CT), an endo-vesical polyp and non-specific nodules in the ascending colon were identified. A colonoscopy was performed, and identified post-irradiation changes, such as scarring and strictures. Following the cystoscopy and biopsy of the endo-vesical polyp, the diagnosis of urothelial carcinoma of the urinary bladder was concluded. The patient underwent a Trans-Urethral Vesical Resection (TURV) procedure and the final diagnosis was G3 papillary urothelial carcinoma, pT1NxMx). Ten bladder instillations with Mitomycin C were administered as adjuvant treatment.

After several months, the patient returned with a mass in the right inguinal region, which was biopsied and subsequently diagnosed as a lymph node metastasis of a non-keratinizing squamous cell carcinoma, of unknown origin. However, given anatomic location, the probability of a metastasis from the previously treated vulvar carcinoma was clinically suspected. A thoraco-abdominal-pelvic CT scan was performed, which identified multiple pelvic, retroperitoneal, and lumbo-aortic adenopathies. The bladder was clear. Systemic treatment with Paclitaxel and Carboplatin (10 cycles) was administered, with only a modest response on the pelvic adenopathies, as assessed by CT imaging. In addition, due to haematological toxicity and peripheral neuropathy, dose de-escalation of the last 3 cycles of chemotherapy was done.

The following year, four months after the completion of the last chemotherapy cycle, the bladder tumour recurred, with extensive invasion of adjacent organs (rectum, pelvic soft tissue). Unfortunately, at that time, patient was no longer a surgical candidate and, palliative treatment and pain control was recommended. Patient's history and clinical evolution are presented in Figure 2.

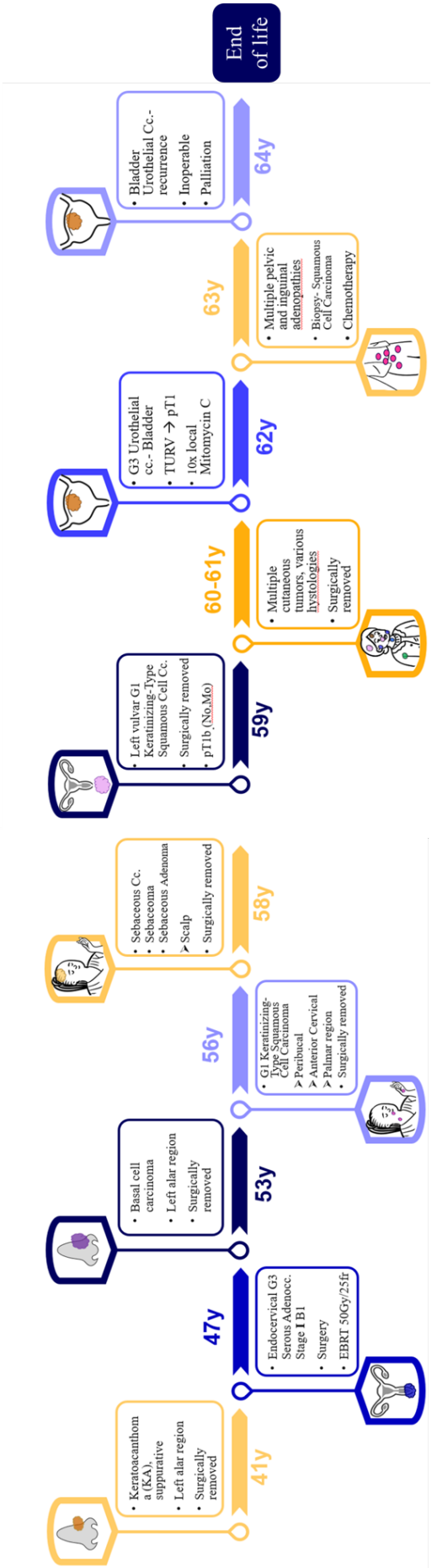

Figure 2. Patient history and evolution; y= years, G1= grade 1; EBRT= External beam radiotherapy; CC= carcinoma

3. Molecular and genetic testing

Given the significant personal and family history, the suspicion of a hereditary cancer syndrome was raised. Immuno-histochemical testing was performed on the resected bladder tumour specimen, revealing loss of nuclear expression of MSH2 and MSH6 proteins involved in DNA repair (mismatch repair deficient), thus indicating a possible microsatellite instability syndrome. The expression of MLH1 and PMS2 proteins was retained. According to the NCCN guidelines (9) the absence of MSH2 and MSH6 staining suggests either a germline *MSH2/EPCAM* pathogenic gene variant or rarely a *MSH6* pathogenic gene variant. In case of a sporadic cancer, the cause would probably have been of somatic origin.

Also, considering the fulfilment of the Amsterdam and NCCN criteria (9,10) (> 3 family members affected by HNPCC-related cancers, at least one first-degree relative and > 2 affected successive generations, with at least 1 case of colorectal carcinoma under the age of 50 and histologically confirmed lesions), a decision was made to perform extensive genetic testing (83-gene Multi-cancer panel, performed at Invitae, USA panel, using peripheric venous blood). The 83 genes involved in most types of hereditary cancers are presented in Table 2. DNA Sequencing and deletion/duplication of the 83 genes was performed, resulting in the identification a germline mutation pathogenic variant in the MSH2 gene, namely c.1861C>T (p.Arg621*), in heterozygous state. This particular non-sense variant usually leads to a premature translational stop signal in the MSH2 gene. It is expected to result in an absent or disrupted protein product. This variant has been submitted to ClinVar database (variation ID 90804), where 16 entries were identified in several patients suspected of Lynch syndrome or other types of hereditary colo-rectal cancer (11). Given the rich family history and the identified germline pathogenic variant, genetic testing was extended to the patient's first-degree relatives, with one out of three descendants carrying the same pathogenic variant in the MSH2 gene.

4. Discussions

The presented case is impressive in terms of its complicated history and long evolution, with the final diagnosis discovered more than 20 years after the initial presentation.

The patient fulfilled all required criteria for Muir-Torre syndrome, a rare subtype of Lynch syndrome. She presented with multiple benign and malignant skin tumours, with over ten histological types, including sebaceous tumours (being essential for the clinical diagnosis of the Lynch syndrome subtype). She also had several visceral cancers – endocervical adenocarcinoma, followed by a vulvar squamous cell carcinoma, which also metastasized into the pelvic and inguinal lymph nodes, and finally the urothelial cell carcinoma of the bladder; genitourinary cancers are present in 25% of Muir Torre syndrome cases(12–15).

Also, the strong family history further reinforces this diagnosis, with multiple relatives across at least four generations affected by different malignancies, including first degree relatives (16). Guided by the Amsterdam criteria for genetic testing in the case of suspected HNPCC syndrome (10), we decided to perform an extensive germline testing of both the patient and the first degree descendants. The genetic testing in this case brought essential information to both the patient, as well as the family, identifying a pathogenic germline variant in the MSH2 gene, thus confirming the germline origin of the MMR deficiency observed in patient's tumour (5).

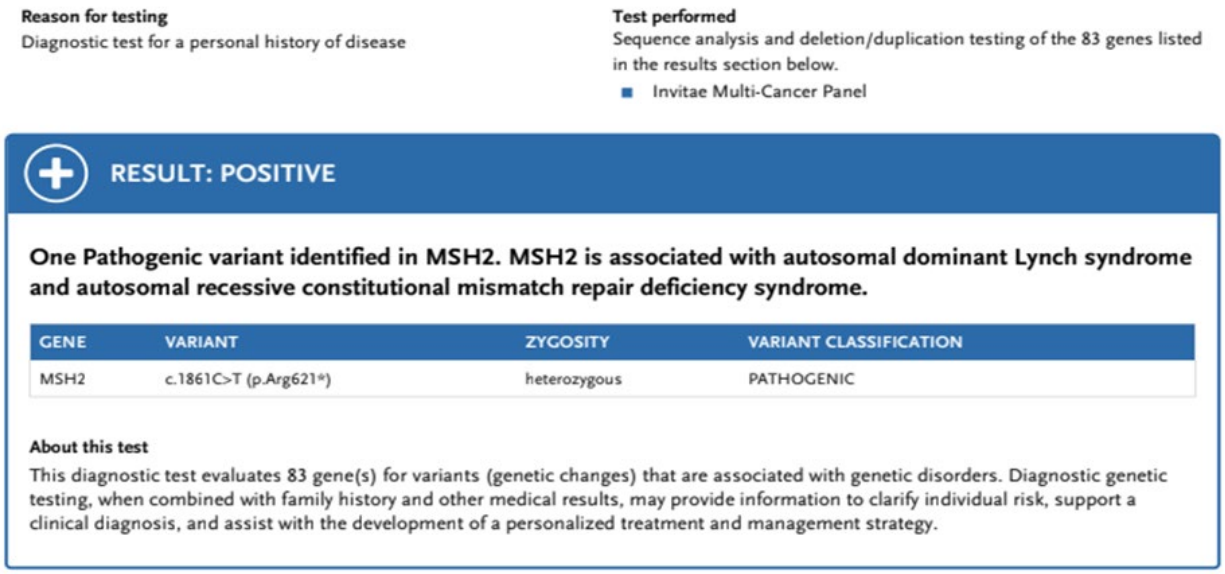

Figure 3. Genetic testing result- germline mutation in MSH2 gene identified.

With such a complex presentation, there were several therapeutic challenges. Notably, the stage IB vulvar carcinoma might have benefited from ipsi- or bilateral inguinal lymph node dissection, and the option of external beam radiotherapy could have been discussed, given the long time since the initial pelvic irradiation (more than 10 years). More so, the urothelial cancer was a high grade, pT1 tumour, which is classified as a high-risk tumour that might have benefited from a more radical surgical treatment (cystectomy), intravesical Bacillus Calmette-Guerin (BCG) or immunotherapy, especially in the context of MSI-high tumours(17). Also, clinical trial screening and enrolment or off-label medication prescription could have been possible and might have offered her a chance to a targeted treatment(18). Additionally, the option of using PET-CT for follow-up in the context of such frequently re-occurring tumours could have been beneficial.

In terms of identified pathogenic variant in healthy relatives, the level of vigilance should be increased. Genetic counselling and sustained screening for the prevention and early detection of cancers for which they may be at risk should be recommended, according to the latest NCCN guidelines(9). Specifically, we made several recommendations to the patient's descendant in which we detected the MSH2 pathogenic variant, regarding the follow-up and surveillance: yearly clinical examinations, colorectal screening by periodic colonoscopy (every 1-2 years), gynecological examination, with pelvic ultrasound and aspiration biopsy every year, from age 30 to 35 years, gastric cancer screening by periodic upper gastro-intestinal endoscopy (every 2-4 years), and regular, frequent skin examination(19). Taking the high risk of both endometrial and ovarian cancer into account, the options of risk-reducing surgical interventions (bilateral prophylactic salpingo-oophorectomy and hysterectomy) were also addressed. Given the family history of breast cancer, which represents an independent risk factor for this type of cancer, yearly breast surveillance was also recommended, starting earlier than in the standard risk population (20,21). More, oral chemoprophylaxis with retinoids (isotretinoin) for cutaneous tumours prevention could be an option for these patients. Other options include subcutaneous Interferon 2alpha and topic applications of retinoids (21–24). A more recent breakthrough in this area are vaccines for immunoprevention of DNA mismatch repair deficient cancers, which show promising results in initial phases(25).

Table 2. The 83- gene panel tested for this case, comprising genes involved in most types of hereditary cancers

ALK	**APC**	**ATM**	**AXIN2**	**BAP1**	**BARD1**	**BLM**	**BMPR1A**
BRCA1	BRCA2	BRIP1	CASR	CDC73	CDH1	CDK4	CDKN1B
CDKN1C	CDKN2A	CEBPA	CHEK2	CTNNA1	DICER1	DIS3L2	EGFR
EPCAM	FH	FLCN	GATA2	GPC3	GREM1	HOXB13	HRAS
KIT	MAX	MEN1	MET	MITF	MLH1	MSH2	MSH3
MSH6	MUTYH	NBN	NF1	NF2	NTHL1	PALB2	PDGFRA
PHOX2B	PMS2	POLD1	POLE	POT1	PRKAR1A		PTCH1
RAD50	RAD51C	RAD51D	RB1	RECQL4	RET	RUNX1	PTEN
SDHAF2	SDHB	SDHC	SDHD	SMAD4	SMARCA4		SDHA
STK11	SUFU	TERC	TERT		TMEM127	TP53	WT1
SMARCE1		TSC1	TSC2	VHL	WRN	SMARCB1	

There are approximatively 200 other cases reported in the literature describing this syndrome, thus emphasizing the particularity of this case (26–31). Without strong evidence for specific treatment or prophylaxis options for these patients, active screening and managing tumours in the early stages seems the best available approach. Novel therapies, such as targeted molecules, immunotherapy, or vaccines, might become a solution in the future. However, given the rarity of this disease, clinical trials are difficult to design and patient enrolment could be challenging, requiring international efforts and long periods of inclusion and follow-up (25,32–34).

5. Conclusions

Muir-Torre syndrome, a rare subtype of the Lynch syndrome, is characterized by microsatellite instability, which causes cancer predisposition in patients who carry pathogenic variants in specific mismatch-repair genes. The case we described follows the typical presentation of this disease, with multiple tumours of various histology, both visceral and cutaneous. Patient management is usually multidisciplinary and tumour-specific, with screening and surveillance essential for the patient and their family.

Abbreviations:
CC – Carcinoma
CT – Computed Tomography
DNA – Deoxyribonucleic acid
G – Grade
Gy – Gray
HNPCC – Hereditary Non-Polyposis Colorectal Cancer
MSI – Microsatelite Instability
MMR – Mismatch Repair
MLH – MutL protein homolog
MSH – MutS homolog
NCCN – National Comprehensive Cancer Network
pT – Pathological tumoral stage
PMS – Mismatch repair endonuclease PMS
TURV – Trans-Urethral Vesical Resection

Statements:
Authors' contributions: AT collected the data and wrote the manuscript; BF, AT, VN participated in patient management, including diagnosis and treatment and manuscript proofing/editing;
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