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A case report of Muir–Torre syndrome (MTS) in a Chinese patient

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Abstract

Background Muir-Torre syndrome is a rare disorder characterized by patients suffering from sebaceous gland tumors or keratoacanthoma and visceral malignancies. More cases have been reported in Europe than in Asia. In this study, we report a case of MTS in China.

Case presentation A 64 -year-old woman presented with a growth on the left upper eyelid noticed 3 months prior. Ancillary examinations include orbital CT, Ultrasound of parotid and submandibular glands, and Ultrasound of the cervical lymph nodes. All showed no clear abnormalities. Eyelid tumors were removed after general anesthesia. Seven months after the operation, a malignant rectal tumor was found. Based on the patient's clinical manifestations, physical signs, and ancillary test findings, this case was ultimately diagnosed as a rare presentation of keratoacanthoma combined with rectal malignancy.

Conclusions This case report describes a rare occurrence of Muir-Torre syndrome (MTS) diagnosed in a patient who presented with a keratoacanthoma of the eyelid and subsequently developed rectal carcinoma. The diagnosis was confirmed through comprehensive clinical evaluation and molecular analysis demonstrating microsatellite instability, consistent with the diagnostic criteria for MTS.

Keywords Keratoacanthoma, Rectal malignancy, Muir-Torre syndrome, MSH2, MSH6, Case report

Introduction

Muir-Torre syndrome (MTS) is an autosomal-dominant condition of genetic origin characterised by tumours in the sebaceous gland or keratoacanthoma that are associated (i.e., arise simultaneously or sequentially) with one or more of various visceral malignant diseases, in particular, colorectal, endometrial, urological, and upper gastrointestinal neoplasms [1]. The first study of Muir-Torre syndrome is dated 1967, when Muir and colleagues described a Maltese man with many primary carcinomas in the colon, duodenum, and larynx who also had keratoacanthomata of the face [2]. In 1976, Reiffers and co-workers reported a patient with a remarkable and informative family history of Muir-Torre syndrome, providing the first description of the autosomal-dominant pattern of inheritance and the variety of clinical presentations [3]. The onset of Muir-Torre syndrome is complex. It is widely believed that the occurrence of MTS is related to mismatch repair (MMR) [4]. The altered MMR genes associated with MTS include Mutator L Homologue (MLH) 1, Mutator S Homologue (MSH) 2, MSH6, Postmeiotic Segregation Increased (PMS) 2 [5]. Muir-Torre syndrome is a rare disease. Its low incidence rate has resulted in limited documented cases. Most clinical reports on Muir-Torre syndrome (MTS) have focused on

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white populations in developed countries [1]. This article presents a case of an elderly female patient with Muir-Torre Syndrome in China.

The purpose of this report is to highlight the importance of clinical awareness of MTS and underscore the role of immunohistochemical analysis in its diagnosis.

Case presentation

A 64-year-old woman presented with a left upper eyelid mass that had been present for 3 months. Her medical history included type 2 diabetes mellitus for 12 years that was well controlled with metformin (0.25 g orally twice a day); hypertension for 10 years that was managed with irbesartan (75 mg orally once daily); and frequent diarrhea and constipation (undiagnosed and untreated). Patient underwent hysterectomy for postpartum hemorrhage 25 years ago. Twenty-five years prior, she underwent a hysterectomy for postpartum hemorrhage. Family history revealed her sister died of ovarian cancer and her father succumbed to a hematologic disorder.

Physical examination revealed no lymph node abnormalities. Corrected distance visual acuity was 20/20 in the right eye and 16/20 in the left eye. Ocular alignment and motility were normal. A full-thickness growth measuring approximately $23 \times 10 \times 4$ mm was observed on the left upper eyelid margin. The growth had a tough texture and obvious ulceration. The color of the lens nucleus was evaluated as NC2. Anterior and posterior segment examinations were otherwise unremarkable (Fig. 1A). CT imaging (Fig. 1D) demonstrated an elevated tumorous lesion on the left upper eyelid. Periocular soft tissues appeared normal bilaterally. Ultrasonography of bilateral parotid and submandibular glands showed no abnormalities. Ultrasound of the cervical lymph nodes revealed no abnormalities.

Following comprehensive clinical evaluation, the patient underwent general anesthesia for surgical intervention comprising three principal components: excision of a left upper eyelid neoplasm, full-thickness eyelid reconstruction via sliding cutaneous flap anterior lamellar restoration with hard palate mucosal posterior lamellar grafting, and palpebral margin reconstruction(Fig. 1B). Pathological examination (Figs. 1C and 100X and X) revealed squamous epithelial papillomatous hyperplasia with keratosis and that the central fovea was enriched in keratinocytes and keratin; Keratoacanthoma (KA) was considered. The pathological results indicate that the tumor did not invade the striated muscle tissue, and no tumor cells were observed outside the resection margin. The patient did not complain of discomfort during regular follow-up after surgery. While comprehensive metastatic evaluation was recommended to exclude systemic dissemination, the patient elected to decline additional diagnostic assessment.

More than 7 months after eyelid surgery, the patient presented with hematochezia. Abdominal computed tomography (CT) demonstrated eccentric mural thickening of the rectum, radiologically suggestive of a neoplastic lesion (Fig. 2A). Based on clinical and imaging findings, rectal tumor was considered. Different from conservative local lesion resection, radical rectal cancer resection was performed with intraoperative findings confirming successful resection. Histopathological evaluation (Figs. 2B and 200X and X) revealed invasive tumor growth into perirectal tissues, characterized by atypical glandular structures embedded within desmoplastic stroma. Notable cytological atypia, pathological mitotic figures, and architectural disorganization supported a diagnosis of moderately to poorly differentiated rectal adenocarcinoma. The tumor breached the muscularis propria layer but exhibited clear surgical margins (proximal, distal, and circumferential), with no lymphovascular invasion or nodal metastasis identified.

Immunohistochemical analysis of DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, PMS2) demonstrated intact nuclear expression of MLH1 (Figs. 2C and 200X and X) and PMS2 (Figs. 2D and 200X and X), with concurrent loss of MSH2 (Figs. 2E and 200X and X) and MSH6 (Figs. 2F and 200X and X) nuclear immunoreactivity.

Discussion and conclusions

We present a case of rectal carcinoma diagnosed following surgical management of an eyelid keratoacanthoma. Postoperative immunohistochemistry testing revealed the absence of MSH2 and MSH6, indicating microsatellite instability. Based on established clinical diagnostic criteria—specifically the concurrence of a sebaceous neoplasm with a visceral malignancy and evidence of mismatch repair deficiency—this case fulfills the diagnosis for Muir-Torre syndrome (MTS) [1].

MTS is a very rare condition, especially among Chinese populations. A single-center conducted at Mayo Clinic (Rochester, MN) demonstrated marked ethnic disparities in MTS prevalence, with the highest incidence observed in Ashkenazi Jewish and Northern European ancestries, contrasted by significantly lower rates in African and Hispanic populations [6]. The first documented Chinese MTS case was reported in 2015, involving a 46-year-old male presenting with a hemorrhagic right upper eyelid nodule of one month's history. Histopathological evaluation confirmed sebaceous carcinoma, with the patient's medical history notable for colon cancer managed by right hemicolectom [7]. Another Chinese patient with MTS reported was in 2021. In this report, the authors described a 41 - year - old man with a history of kidney transplantation. While undergoing immunosuppressive therapy, the patient witnessed a rapid expansion of the

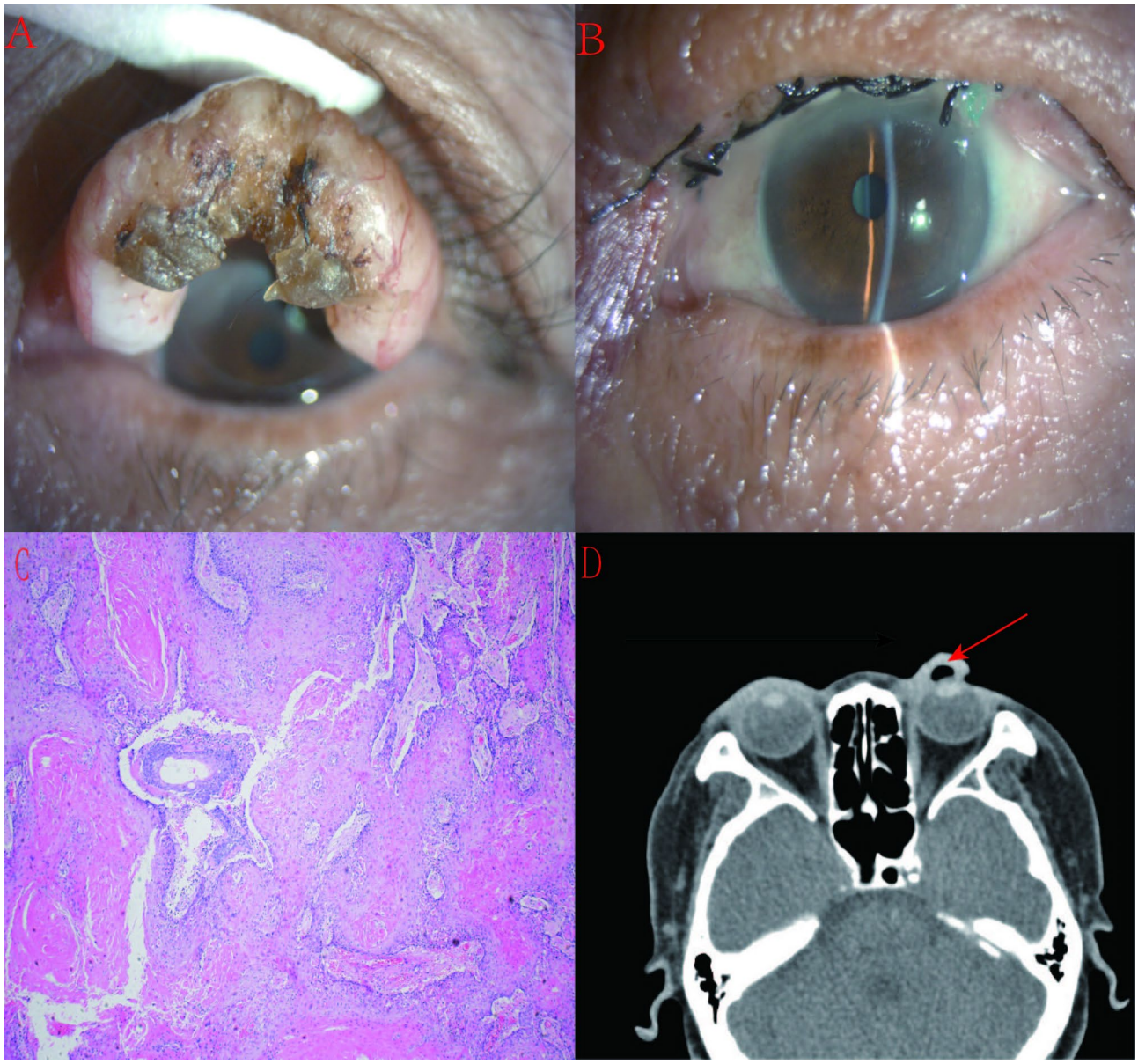

Fig. 1 (**A**) The left upper eyelid exhibits a full-thickness tarsal lesion (**B**) Post-surgical imaging confirms anatomical restoration of the eyelid margin following en bloc excision (**C**) Histopathological evaluation demonstrates squamous epithelial hyperplasia with a papillomatous growth pattern, accompanied by focal parakeratosis. A central keratin-filled crypt containing densely packed keratinocytes and stratified keratinous material is observed (**D**) A well-circumscribed mass on the left upper eyelid

nodule on the anterior chest. Histological assessment identified sebaceous carcinoma, prompting systemic malignancy screening that revealed a synchronous sigmoid colon adenocarcinoma.

Immunohistochemical profiling demonstrated complete loss of MSH2 and MSH6 nuclear expression with preserved MLH1 and PMS2 reactivity, while microsatellite instability (MSI) testing revealed mismatch repair (MMR) gene alterations [8].

To date, these remain the only reported cases of Muir-Torre syndrome (MTS) in individuals of Chinese descent. Both patients manifested the pathognomonic triad of cutaneous sebaceous neoplasia, visceral adenocarcinoma (colorectal origin), and molecularly confirmed mismatch repair (MMR) deficiency.

In this clinical presentation, a patient sought medical attention for an eyelid neoplasm, which was histopathologically confirmed as keratoacanthoma following surgical excision. Literature indicates that cutaneous lesions may be the first sign of MTS in 41% of these patients [9]. Based on this evidence, the emergence of sebaceous neoplasms or keratoacanthomas warrants comprehensive

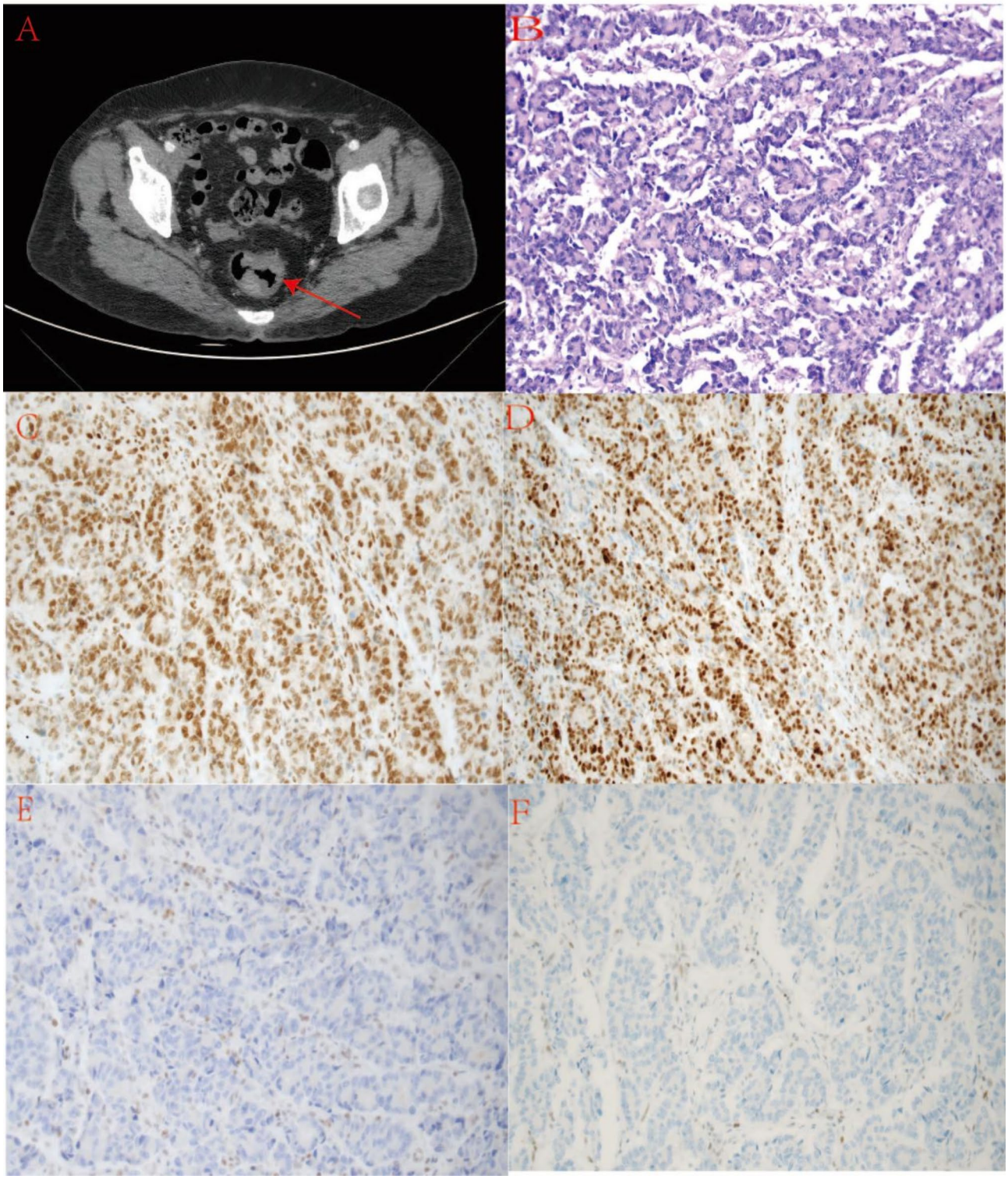

Fig. 2 (**A**) Cross-sectional imaging reveals eccentric mural thickening of the rectal wall with an irregular soft tissue mass exhibiting intraluminal protrusion. (**B**) Histopathological analysis demonstrates infiltrative neoplastic glands within desmoplastic stroma, displaying architectural complexity characterized by cribriform patterning and anastomosing glandular structures. The malignant epithelium exhibits high-grade cytologic atypia with nuclear pleomorphism and prominent nucleoli (**C**) Immunohistochemical profiling shows retained nuclear immunoreactivity for MLH1 protein within tumor cells (**D**) Preserved nuclear expression of PMS2 protein is observed (**E**) Loss of nuclear MSH2 protein expression is evident (**F**) Absent nuclear MSH6 protein expression

systemic evaluation for potential visceral malignancies. Postoperatively, the patient was advised to undergo visceral tumor screening, which was declined due to conomic constraints. Seven months after the operation, the patient presented with hematochezia, and a rectal mass was found. Subsequent histopathological analysis confirmed rectal adenocarcinoma. Looking back on the patient's previous medical history, she had suffered from diarrhea and constipation for many years but did not seek medical treatment. Therefore, it could not be determined whether the intestinal lesions occurred after the eyelid lesions. Retrospective review of medical history revealed chronic bowel dysfunction (alternating diarrhea and constipation) spanning several years, though definitive temporal correlation between intestinal pathology and initial cutaneous presentation remains undetermined. Immunohistochemical profiling of the rectal carcinoma demonstrated deficient mismatch repair (dMMR) status characterized by retained nuclear expression of MLH1 and PMS2 with loss of MSH2 and MSH6 expression. Combined with the patient's family history of ovarian malignancy in a sibling, these findings support a diagnosis of MTS in this elderly Chinese female presenting with keratoacanthoma-associated visceral malignancy. According to the Mayo Muir–Torre syndrome risk score algorithm, the score of this patient is 2. Current clinical guidelines by Roberts et al. recommend mismatch repair (MMR) protein immunohistochemical analysis for patients scoring ≥ 2 on this risk stratification tool. Such evaluation facilitates definitive diagnosis, comprehensive disease staging, and formulation of personalized surveillance and therapeutic strategies [6].

MTS is a mostly autosomal dominant, characterized by an association with sebaceous skin tumors and visceral tumors. This disorder stems from germline mutations in DNA mismatch repair (MMR) genes - notably MLH1, PMS2, MSH2, and MSH6 - whose functional deficiencies induce microsatellite instability (MSI) through impaired DNA error correction. Notably, approximately 33% of MTS cases demonstrate MSI-negative status, defining a molecularly distinct subtype designated as MTS type II (constituting ~ 35% of cases). This variant displays distinct molecular characteristics with predominant autosomal recessive transmission patterns [10].

The definitive diagnostic criteria for MTS require the presence of one or more cutaneous sebaceous neoplasms or keratoacanthomas along with at least one visceral malignancy. Colorectal cancer is the most common visceral neoplasm associated with MTS, followed by endometrial cancer, urinary tract neoplasms, upper gastrointestinal cancer, and pancreatic cancer [1]. Immunohistochemical (IHC) evaluation of mismatch repair (MMR) proteins serves as the primary screening modality for MTS. Individual MMR protein deficiencies demonstrate variable positive predictive values (PPVs): MSH2 (55%), MLH1 (88%), and MSH6 (67%). Notably, the co-loss of specific mismatch repair protein complexes—particularly the combined deficiency of MLH1 and MSH6 or the triad deficiency of MLH1, MSH2, and MSH6—demonstrates 100% diagnostic positive predictive value, serving as a molecularly definitive confirmation of Muir-Torre syndrome [11].

The pathogenesis of MTS is primarily attributed to germline mutations in mismatch repair (MMR) genes, with MSH2, MLH1, MSH6, and PMS2 constituting the predominant molecular targets. A small number of sporadic cases have been seen in patients who underwent organ transplants and received immunosuppressants [12]. Furthermore, environmental carcinogenic cofactors—including therapeutic irradiation, ultraviolet (UV) radiation exposure, and occupational ionizing radiation—have been implicated in tumorigenesis among genetically predisposed MTS patients [13].

Given the rarity of MTS, heightened clinical vigilance is imperative due to its strong association with synchronous or metachronous malignancies. Beyond assessing typical familial cancer predisposition and personal oncologic history, systematic immunohistochemical (IHC) evaluation of tumor specimens is critical to identify MTS in patients with uninformative family histories. Immunohistochemical staining for MMR gene products has been advocated for screening MTS in Sebaceous gland tumors or Keratoacanthomas [14]. In this case report, molecular characterization of the rectal adenocarcinoma in an elderly Chinese female revealed concurrent loss of MSH2 and MSH6 expression, a pathognomonic molecular profile consistent with MTS-associated mismatch repair deficiency. This immunohistochemical pattern aligns with established genotype-phenotype correlations documented in MTS literature.

In summary, this report describes a case of MTS in an elderly Chinese female presenting with synchronous eyelid keratoacanthoma and rectal adenocarcinoma. Immunohistochemical evaluation of the colorectal neoplasm revealed complete loss of nuclear MSH2 and MSH6 expression, confirming microsatellite instability (MSI) status as the molecular hallmark. Correlating the patient's familial oncologic history (including a sister with ovarian carcinoma) with characteristic dual cutaneous-visceral tumorigenesis establishes definitive MTS diagnosis. For patients with MTS and their family members, timely treatment, regular follow-up, and genetic assessment should be carried out. While advanced genomic sequencing represents the diagnostic gold standard, mismatch repair protein immunohistochemistry remains a clinically validated, economically feasible first-tier screening modality endorsed by international consensus guidelines. This case exemplifies the pivotal role

of immunohistochemical profiling in resource-conscious settings for timely identification of hereditary cancer syndromes.

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Author contributions
Jing Wang was responsible for writing and editing the manuscript, Xin Qi was in charge of collecting data, Kunning Zhang was responsible for organizing the pathological data, and Wei Zhang was responsible for revising the manuscript and verifying the case materials.

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Data availability
The data and materials are available in the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient granted permission to publish this information. Written informed consent for the publication of this case-report was obtained from the patient.

Competing interests
The authors declare no competing interests.

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