Painless perianal mucinous adenocarcinoma: A case report and literature review

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Abstract. Painless perianal mucinous adenocarcinoma (PMA) is characterized as a rare malignant tumor of the anal canal and rectum; its incidence rate is extremely low, and it has atypical clinical manifestations. In the present case report, a 79-year old male patient is described who presented with a painless perianal mass that had been present for 15 days. Perianal B-ultrasound examinations revealed a well-circumscribed hypoechoic mass with a maximum diameter of 3.31 cm. A pathological examination of the resected tumor specimen revealed that the tumor exhibited an expansive nodular growth pattern, accompanied by irregular infiltration of glandular structures and extensive secretion of extracellular mucus. The columnar and goblet cells presented with low-grade intraepithelial neoplasia. Immunohistochemistry examinations showed positive staining for cytokeratin (CK) 7, CK20, caudal type homeobox 2 and mucin 2. The molecular test results suggested a KRAS p. G12d activating mutation. The pathological diagnosis was PMA. The patient underwent radical local wide resection 1 month later, and no recurrence or metastasis was observed during a follow-up period of 12 months. The present case report provides a real-world reference for the clinical diagnosis, selection of treatment plans and evaluation of the prognosis of painless PMA.

Introduction

Perianal mucinous adenocarcinoma (PMA) is a rare disease and accounts for <5% of all gastrointestinal malignancies (1,2). Its occurrence is associated with chronic perianal infections such as anal fistula and Crohn's disease (3). The common symptoms are recurrent perianal abscess, perianal pain and bleeding (4-6), and the manifestation of a painless perianal mass is rare (7) with no clear data in the literature. As the early symptoms of PMA overlap with benign conditions such as perianal abscesses and anal fissures, the pathological biopsy is also affected by the presence of mucus alone and may result in a missed diagnosis (1,7). The pathological features of PMA are similar to those of colorectal mucinous adenocarcinoma, including invasive glands lined with columnar cells that secrete abundant extracellular mucus (7,8). A KRAS gene mutation is common in colorectal mucinous adenocarcinoma (CMA) (9), but to the best of our knowledge, there are fewer reports of KRAS gene mutations in PMA (5). There is no standardized treatment protocol, and the main treatment techniques used in a few cases have been radical surgery, adjuvant radiotherapy and chemotherapy, and partial wide resection (7,10,11). Studies on painless PMA are relatively scarce, and research on its pathogenesis, diagnostic procedures and prognosis assessment is limited. There is a lack of systematic analysis of painless cases without chronic inflammation or a history of fistula, which leads to a lack of understanding and diagnostic experience among doctors for this special type of case.

The painless PMA in the present case report was unique: The patient had no history of chronic perianal diseases such as anal fistula or Crohn's disease, and there were no clear chronic inflammatory or fistula-related pathogenic factors, which are notably different from the disease backgrounds of the majority of patients with PMA. Due to the presence of atypical clinical manifestations and based on auxiliary examinations, painless PMA is easily misdiagnosed as a benign tumor, resulting in a lack of further examinations and the inability to perform the extended radical resection. In the present case report, relevant studies (1,2,7,9) have been combined to analyze the clinical, pathological, immunohistochemical, treatment and prognosis characteristics of this disease, aiming to improve the understanding among doctors and pathologists.

Case report

A 79-year old male patient with a 15-day old painless perianal mass was admitted to the First People's Hospital of Xiaoshan (Hangzhou, China) in January 2024. While conducting an

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anal examination in the lithotomy position, a mass under the epidermis was palpated. The mass was located between the 12 O'clock and 2 O'clock directions, 3.0 cm away from the anal margin. It had a volume of 4.0x3.0x2.0 cm, clear boundaries, soft texture and no notable tenderness or fluctuation sensation. Bilateral superficial inguinal lymph nodes were not enlarged. Digital rectal examination showed no anal fistula or ulcer, and smooth rectal mucosa. Additionally, no other mass was touched, and no blood or purulent discharge was observed on the glove of the examining physician. Colonoscopy of the patient revealed no abnormalities in the colon. A B-ultrasound examination revealed a low heterogeneous echogenic structure (3.31x1.90x1.77 cm) on the left side of the anal canal. The area had distinct boundaries and a regular shape, with no notable blood flow signal (Fig. 1); thus, the mas was considered to be a benign tumor. Detection of tumor serological markers was performed by following the manufacturer's instructions (Abbott Trading (Shanghai) Co., Ltd.) showed that squamous cell carcinoma-associated antigen was 0.92 ng/ml (normal range <1.50 ng/ml), AFP was 0.92 ng/ml (normal range, 0.89-8.78 ng/ml), sugar chain antigen 125 was 5.80 U/ml (normal range, 0-35 U/ml), carbohydrate antigen 199 was 6.70 U/ml (normal range, 0-37 U/ml) and carcinoembryonic antigen was 3.94 ng/ml (normal range, 0-5 ng/ml). The normal ranges of all reagents were provided by Abbott Trading (Shanghai) Co., Ltd. and verified by the Clinical Laboratory Department of the First People's Hospital of Xiaosha, Hangzhou, Zhejiang.

Medical history. The patient was previously healthy and did not have a history of any disease such as cardiovascular or cerebrovascular diseases, type 2 diabetes mellitus, chronic kidney disease, chronic bronchitis, bronchial asthma, chronic gastritis, chronic diarrhea or chronic pancreatitis. The patient denied experiencing anal fistula, hemorrhoid disease or any other surgical history. The patient also did not have a family history of hereditary or similar diseases.

The preoperative diagnosis was a perianal mass and the lesion was resected under general anesthesia. During the operation, a mass ~4.0x3.0 cm in size was found; it had distinct boundaries and appeared as a capsule. It was movable and found between the 12 O'clock and the 2 O'clock position in the lithotomy position, 3 cm away from the anal margin. It did not involve the anal canal or the rectal wall. A gross pathological examination revealed soft, gray-yellow tissue with a volume of 3.5x3.0x3.0 cm, with a cystic, solid cut surface and jelly-like substance inside

The tissue was fixed with 10% neutral formalin for 24 h at 25˚C and embedded in paraffin. Next, serial sections (3-μm thick) were prepared and subjected to hematoxylin and eosin (H&E) staining (Shanghai Rongbai Biological Technology Development Co., Ltd., and Sinopharm Chemical Reagent Co., Ltd. for 3 h at 25˚C. The samples were observed using a light microscope. Microscopic examination revealed a nodular, expansile growth of the tumor within fibrous and striated muscle tissue, irregular glands secreting large amounts of mucus (Fig. 2) and the columnar and goblet cells presenting with low-grade intraepithelial neoplasia (Fig. 3). The tumor margin was negative under the microscope.

Immunohistochemistry (IHC) analysis was performed using an EnVision IHC kit (polymer method; cat. no. KIT-0014;

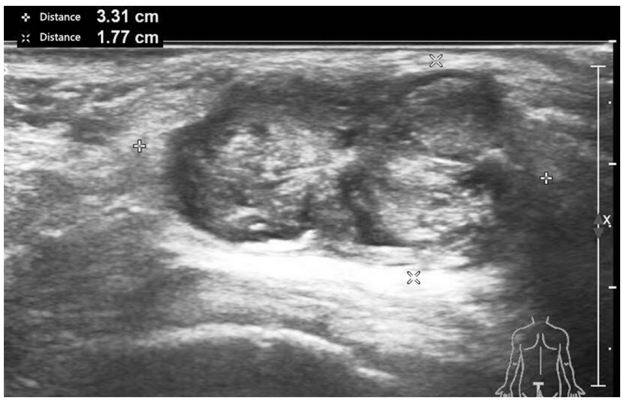

Figure 1. B-ultrasound examination showing a low heterogeneous echogenic light 3.31x1.90 x 1.77 cm in size and with a clear boundary detected on the left side of the anal canal. (Between the two + and between the two x indicates the length and short diameter of the mass, respectively.)

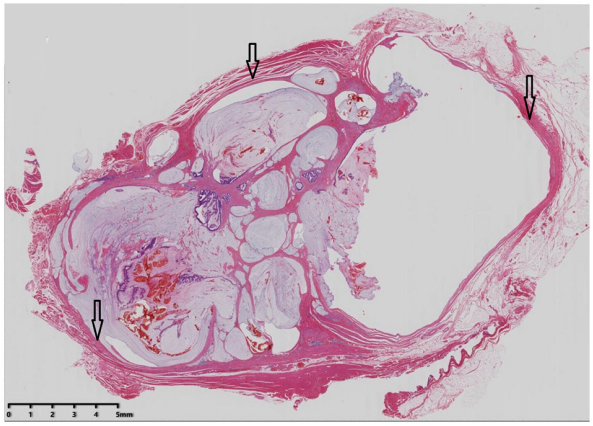

Figure 2. Microscopic image showing a well-circumscribed and nodular tumor (Black arrow), with abundant mucus secretion (magnification, 4x; scale bar, 5 mm; hematoxylin and eosin staining)

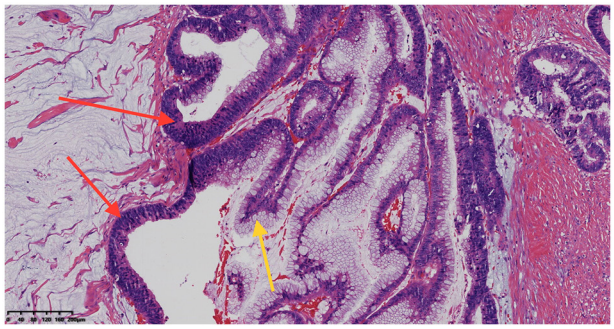

Figure 3. Microscopic image showing low-grade glandular epithelium with cells showing columnar (red arrows) and goblet (yellow arrows) changes. (magnification, 100x; scale bar, 200 μm; hematoxylin and eosin staining).

Fuzhou Maixin Biotechnology Development Co., Ltd.) using primary antibodies (incubated for 50 min at 25˚C) purchased from Beijing Zhongshan Jinqiao Biological Co., Ltd. and Fuzhou Maixin Biotechnology Development Co., Ltd., to target the following proteins (pre-diluted working solutions unless otherwise indicated): CK7 (1:200;

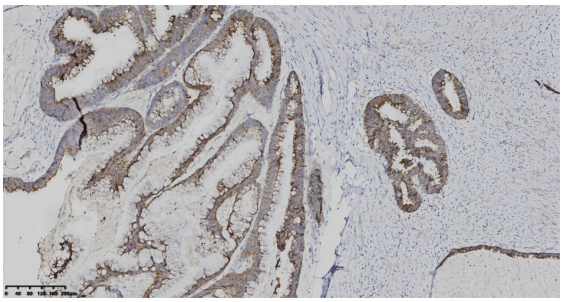

Figure 4. Immunohistochemical staining revealing that the tumor cells are positive for cytokeratin 7 (brown staining; hematoxylin counterstain for nuclear blue staining; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit).

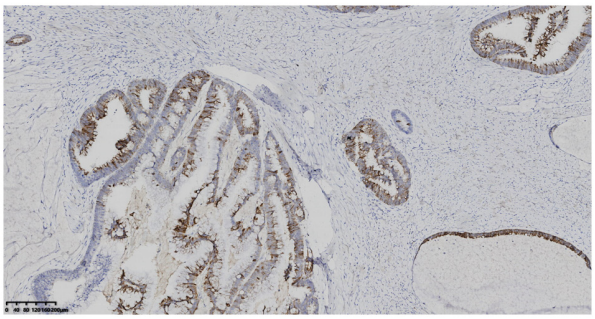

Figure 5. Immunohistochemical staining revealing that the tumor cells are positive for cytokeratin 20 (brown staining; hematoxylin counterstain for nuclear blue staining; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit).

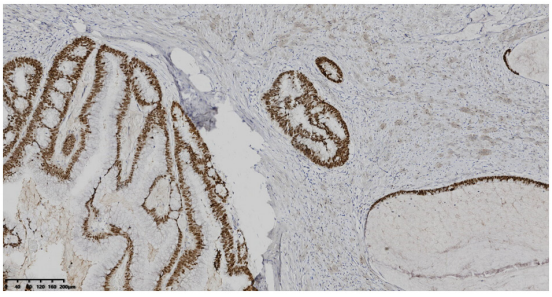

Figure 6. Immunohistochemical staining revealing that the tumor cells are positive for caudal type homeobox 2 (brown staining of nuclei; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit)

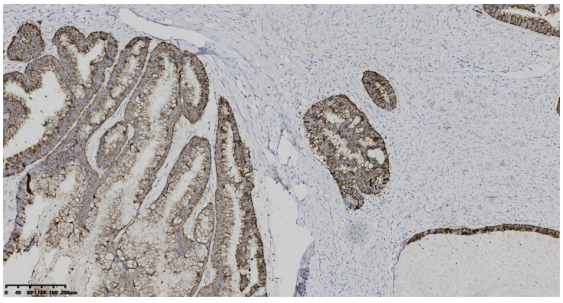

Figure 7. Immunohistochemical staining revealing that the tumor cells are positive for mucin 2 (brown staining; hematoxylin counterstain for nuclear blue staining; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit).

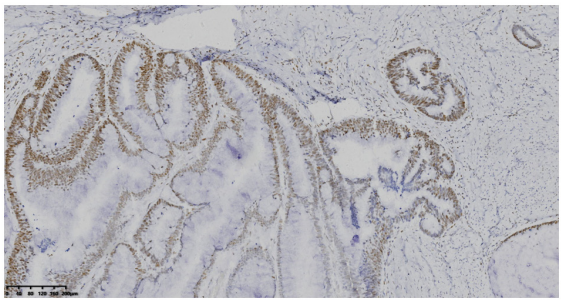

Figure 8. Immunohistochemical staining revealing that the tumor cells are positive for MLH1 (brown staining of nuclei; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit)

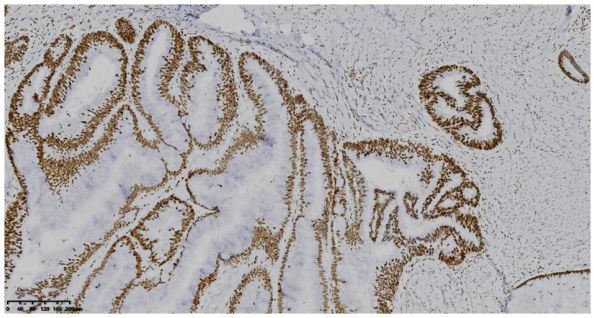

Figure 9. Immunohistochemical staining revealing that the tumor cells are positive for MSH2 (brown staining of nuclei; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit)

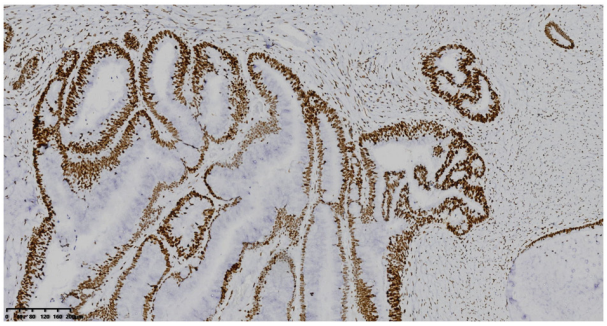

Figure 10. Immunohistochemical staining revealing that the tumor cells are positive for MSH6 (brown staining of nuclei; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit)

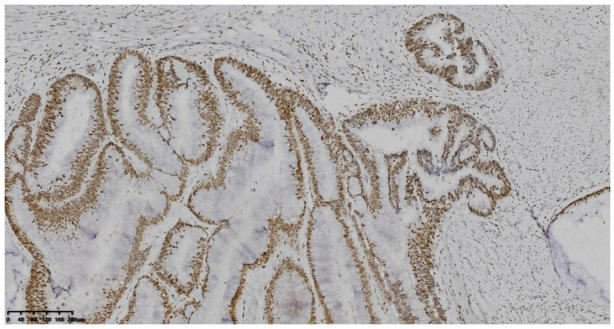

Figure 11. Immunohistochemical staining revealing that the tumor cells are positive for PMS2 (brown staining of nuclei; magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit)

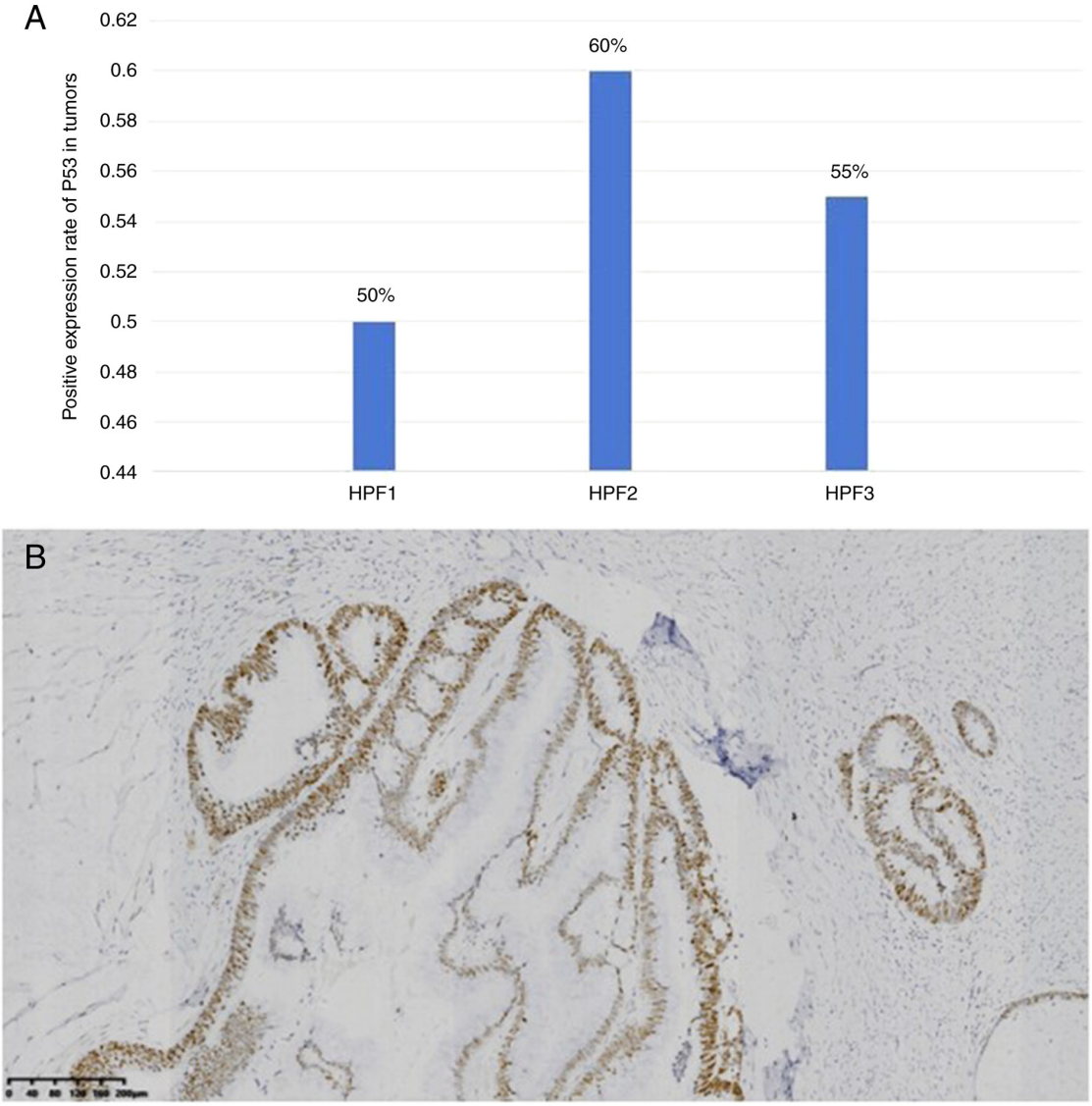

Figure 12. (A) Quantitative analysis of p53positive cells. Data represent the mean percentage of positive cells in 3 HPFs. (B) Representative immunohistochemical staining of p53 in tumor cells, showing a 55% positive nuclear staining rate (brown nuclei; original magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit). HPF, high-power field.

cat. no. ZM-0071), CK20 (1:200; cat. no. ZA-0574), CDX2 (working fluid; cat. no. RMA-0631), Mucin 2 (MUC2; working fluid; cat. no. ZM-0392), MutL homolog 1 (MLH1; 1:100; cat. no. MAB-0838), MutS Homolog 2 (MSH2; 1:200; cat. no. MAB0836), MutS Homolog 6 (MSH6; 1:200; cat. no. MAB-0831), Mismatch repair endonuclease PMS2 (PMS2; 1:200; cat. no. RMA-0775), p53 (1:100; cat. no. ZM-0408) and Ki-67 proliferation index (1:200; cat. no. ZM-0167). IHC sections were observed under a light microscope without software analysis. IHC analysis showed positive expression of CK7, CK20, CDX2 and MUC2 (Figs. 4-7), MLH1, MSH2, MSH6 and PMS2 (Figs. 8-11). The positive expression rate of p53 was 55% (Fig. 12A-B), and the Ki-67 proliferation index was 33% (Fig. 13A and B). The methods described in the case report are the same for the immunohistochemical staining shown in Figs. 8-12 (MLH1, MSH2, MSH6, PMS2 and p53), and this standardized IHC protocol was also used for the other IHC stains (CK7, CK20, CDX2, MUC2 and Ki-67) reported in the present study. Immunohistochemical analysis was performed using the EnVision IHC kit (polymer method; cat. no. KIT-0014; Fuzhou Maixin Biotechnology Development Co., Ltd.) with primary antibodies targeting MLH1, MSH2, MSH6, PMS2, and p53; these primary antibodies were obtained from Beijing Zhongshan Jinqiao Biological Co., Ltd. and Fuzhou Maixin Biotechnology Development Co., Ltd., with specified dilutions for each antibody (MLH1, 1:100; MSH2, 1:200; MSH6, 1:200; PMS2, 1:200; p53, 1:100). The primary antibody incubation step was carried out at 25˚C for 50 min for all targeted proteins in Figs. 8-12. Following the antibody incubation and subsequent kit-based staining procedures, the prepared IHC sections were examined directly under a light microscope and no software-based image or quantitative analysis was conducted for the initial qualitative staining assessment. For p53 (Fig. 12), additional quantitative analysis was performed by calculating the mean percentage of positively stained cells across three high-power fields (HPFs) to determine a 55% positive nuclear staining rate reported for the tumor cells. All

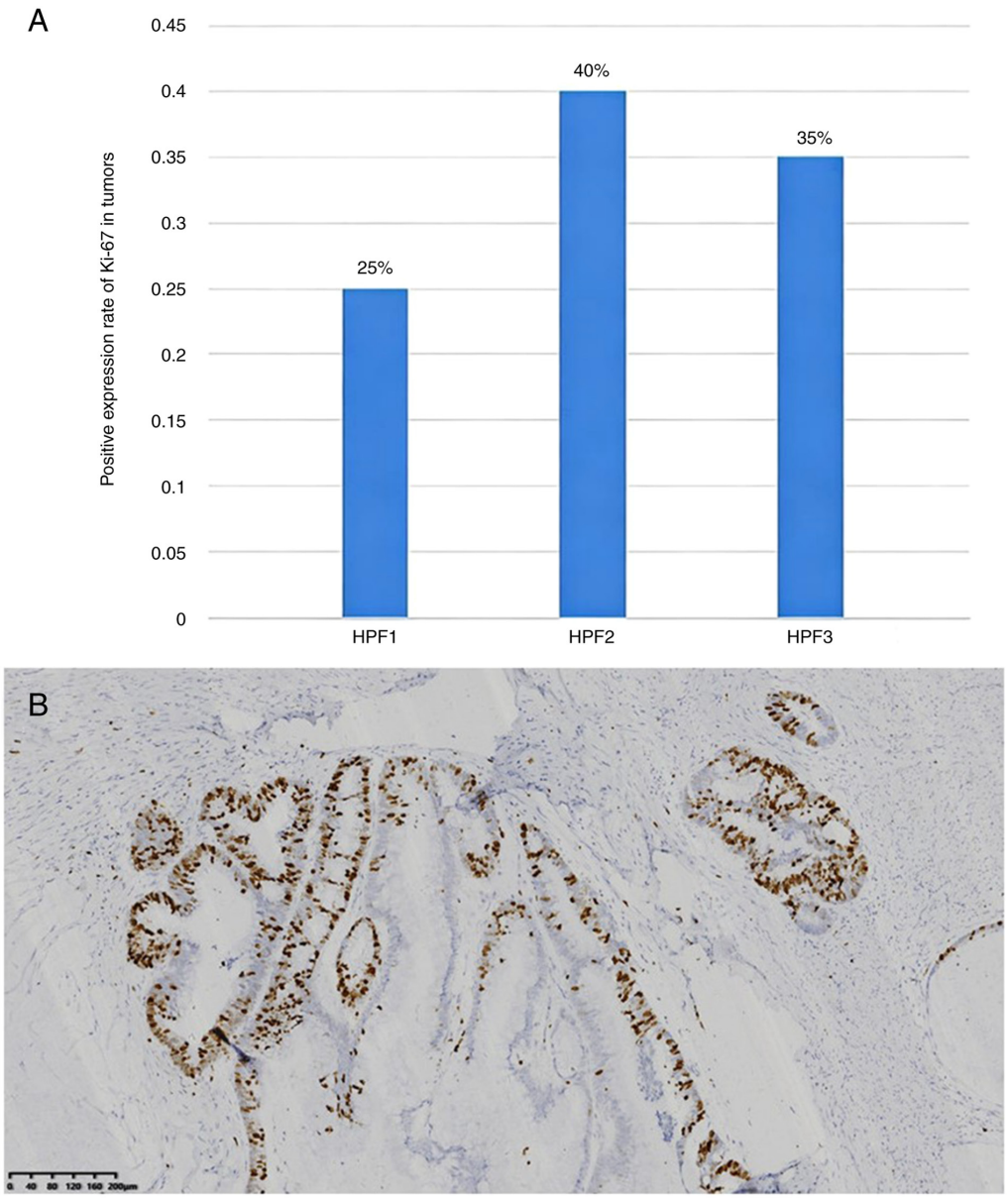

Figure 13. (A) Quantitative analysis of Ki67 proliferation index. Data represent the mean percentage of positive cells in 3 HPFs. (B) Representative immunohistochemical staining of Ki67 in tumor cells, showing a proliferation index of 33% (brown nuclear staining; original magnification, 100x; scale bar, 200 μm; EnVision immunohistochemistry kit). HPF, high-power field.

staining for the proteins in Figs. 8-12 utilized hematoxylin (for 3 min at 25˚C) as a counterstain, which produced blue nuclear staining to contrast with the brown cytoplasmic/nuclear staining indicative of positive antibody binding for the target proteins. The stained sections were imaged at a magnification of 100x, with a 200 μm scale bar included for all micrographs presented in Figs. 8-12B.

Molecular testing was performed by KingMed Diagnostics (next-generation sequencing; Illumina sequencing platform, reference genome: GRCh37/hg19). Sample Preparation Reagents and Verification Methods. Reagents for sample preparation used in the present study are summarized in Table I. Specifically, for nucleic acid extraction from FFPE samples, the One-step extraction (High-sensitivity FFPE Genomic DNA Kit; cat. no. RC1102) was purchased from Kaishuo Biotechnology (Xiamen) Co., Ltd. Library construction and hybridization were performed using the products developed by NanJing Vazyme Biotech Co., Ltd. (VAHTS Universal Plus DNA Library Prep Kit V4). Its composition related to library construction and hybridization is specified in detail as follows: For hybridization, the core reagents include a set of biotinylated DNA/RNA capture probes (120-150 bp), Human Cot-1 DNA and Universal blocking oligos (serving as blocking reagents), high-salt hybridization buffer containing formamide, low-stringency wash buffer (2x SSC; 0.1% SDS), high-stringency wash buffer (0.1x SSC; 0.1% SDS), streptavidin-coated magnetic beads and elution buffer (0.1 M NaOH or Tris-HCl); for library construction, the required reagents consist of fragmentation enzyme, T4 DNA polymerase, Klenow fragment, T4 polynucleotide kinase (for DNA fragmentation and end repair), Klenow fragment (3'→5' exo-) and T4 DNA ligase (for A-tailing and adapter ligation), as well as dual-indexed sequencing adapters (with UMIs), high-fidelity DNA polymerase, dNTP mix (dATP, dTTP, dCTP, dGTP)

Table I. Reagents for sample preparation

Reagent application	Kit name	Cat. no./specification	Supplier
Nucleic acid extraction (FFPE samples)	One-step extraction (High-sensitivity FFPE Genomic DNA Kit)	RC1102	Xiamen Biosan Biotech Co., Ltd.
Library construction and hybridization	Jinyu In-house LDT Solid Tumor Mini panel	No cat. no. (in-house reagent)	KingMed Diagnostics
Sequencing	NovaSeq 6000 S1 v1.5 Kit	20028317	Illumina, Inc.

Table II. Results of genetic testing.

Genes	Nucleotide changes	Amino acid changes	Frequency of variation	Classification of variation	Targeting/ immunization treatment options
KRAS	c.35G>A	p.G12D	15.10%	I	NA
BRAF	ND	NA	NA	NA	NA
MLH1	ND	NA	NA	NA	NA
MSH2	ND	NA	NA	NA	NA
MSH6	ND	NA	NA	NA	NA
NRAS	ND	NA	NA	NA	NA
NTRK1	ND	NA	NA	NA	NA
PIK3CA	ND	NA	NA	NA	NA
PMS2	ND	NA	NA	NA	NA
POLE	ND	NA	NA	NA	NA
RET	ND	NA	NA	NA	NA
POLD1	ND	NA	NA	NA	NA
AKT1	ND	NA	NA	NA	NA
ARAF	ND	NA	NA	NA	NA
RAF1	ND	NA	NA	NA	NA
FGFR1	ND	NA	NA	NA	NA
FGFR2	ND	NA	NA	NA	NA
FGFR3	ND	NA	NA	NA	NA

ND, not detected; NA, not mentioned; MLH1, MutL homolog; MSH2, MutS homolog 2; MSH6, MutS homolog 6; NRAS, NRAS proto-oncogene; NTRK1, neurotrophic receptor tyrosine kinase 1; PMS2, mismatch repair endonuclease PMS2; POLE, DNA polymerase ε; RET, RET proto-oncogene; POLD, DNA polymerase δ; ARAF, A-Raf proto-oncogene.

and primer mix (for library amplification). In addition, quality control reagents including qPCR master mix with reference standards and fragment analyzer reagents were also used in the whole process to ensure the reliability of the experiment. The NovaSeq 6000 S1 v1.5 Kit (cat. no. 20028317) from Illumina, Inc. was employed for sequencing.

Methods for verification of processed sample quality/integrity. The nucleic acid concentration and library concentration of the processed samples were verified using the Qubit assay to ensure that the samples met the requirements for subsequent sequencing and analysis.

Sequencing type. Next-generation sequencing was adopted as the sequencing type, with a read length and sequencing mode of 2x150 bp paired-end sequencing.

Sequencing platform. The Illumina NovaSeq 6000 platform was used for sequencing experiments.

Final library loading concentration and quantification method. For the Illumina NovaSeq 6000 platform, the final library loading concentration was set to 1 nM, and the concentration was quantified by the Qubit assay.

Analysis revealed a KRAS mutation, 35G>A p. G12d, with a mutation frequency of 15.1% (Table II). MSI testing was stable. The final diagnosis was confirmed as PMA, pathological tumor 3, node 0, metastasis 0 (pT3N0M0), Stage IIA

Treatment and follow-up. After the first operation, the doctor found that the tumor boundary was distinct and covered. The pathological examination showed no residual cancer cells at the resection edge. The doctor was not knowledgeable about

the precise postoperative examination selection for malignant tumors. Therefore, only the enhanced computed tomography (CT) scanning of the upper abdomen of the patient and the middle part of the lower abdomen was performed and magnetic resonance imaging (MRI) was omitted. The results revealed soft tissue swelling in the perianal area after the surgery. The size, shape and density of the liver, spleen, gallbladder, pancreas, bilateral ureters and bladder were normal, and no significant thickening of the rectal wall was found. Small cysts and stones were found in the bilateral kidneys.

At that time, the clinician discharged the patient following the tumor resection, and the patient recuperated at home while awaiting the results of the routine pathological examination. After a pathological diagnosis confirmed the perianal tumor to be malignant, the clinician determined that the initial surgical procedure had merely involved the resection of the lesion under a benign tumor presumption, resulting in an inadequate oncologic safety margin. Concurrently, the age of the patient (79 years) was not suitable for immediate surgery, therefore sphincter-preserving local extended radical resection was performed 1 month after the diagnosis of PMA. The surgeon made a circular incision on the surface of the skin 4.0 cm from the perimeter of the previous surgical scar, cut the subcutaneous and adipose tissue of the skin and extended the resection of the previous surgical scar and surrounding tissue, inward to the external anal sphincter. Frozen section examination is used during radical resection, and the procedure is as follows: i) The pathology department verified the specimen and requisition form, then macroscopically selected the lesion tissue. ii) The tissue was embedded in optimal cutting temperature compound and frozen to a hard block at -25˚C. iii) Sections that were 5 μm thick were prepared and rapidly fixed with 95% ethanol (25˚C; 1-2 min). iv) Rapid H&E staining and mounting was preformed (25˚C; 8 min). v) A pathologist performed rapid microscopic diagnosis, issues an intraoperative report and informed the surgeon. Upon examining frozen sections of the surgical margin, no cancer tissue was found.

Pathological examination of the resected specimen (performed byhF&E staining and light microscopy observation) showed focal chronic inflammatory cell infiltration (predominantly lymphocytes and plasma cells) in the fibroadipose tissue, and histological evaluation of the surrounding surgical margins revealed no residual tumor cells, and no vascular or lymphatic invasion, indicating a negative margin. The comprehensive evaluation included postoperative clinical assessment (physical examination, routine laboratory tests and ECOG score), contrast-enhanced CT/MRI of the chest, abdomen and pelvis for excluding local and distant metastasis, pathological TNM staging and risk factor analysis. The patient did not require any additional treatment, including radiotherapy or chemotherapy. During the postoperative period (≤30 days of surgery), the patient had normal stool passage, no abnormal anal discharge and no soiling. Recurrence or metastasis was not detected at the 12-month follow-up.

Discussion

PMA is a rare disease and accounts for <5% of all gastrointestinal malignancies (1,2). A literature summary from 1990-2024 by Gkegkes *et al* (7) revealed that among the 150 cases analysed in Gkegkes' study, the average age of patients with PMA was 60.5 years, and 82.7% were men (men to women ratio, 4.77:1.00). The majority of cases were associated with chronic anal fistula or Crohn's disease (disease duration, 5-20 years). Commonly reported symptoms were perianal pain, bleeding or recurrent abscess (7). Other study has reported that anal fistulas may become malignant 2 years after its formation (12), however the patient in the present case report had no definite history of anal fistula, and only a painless mass was found that was 15 days old. This suggests that there may be the presence of a subclinical glandular malignant process, and further emphasizing the need for clinicians to be alert to atypical perianal masses.

Regarding the pathogenesis, PMA may be associated with chronic inflammation, the upregulation of MUC2 and mutations in the Ras/MAPK pathway (8,9,13,14). MUC2 is a glycoprotein secreted by intestinal goblet cells, and its upregulation is closely associated with CMA (13). KRAS gene mutation is a common carcinogenic mechanism, and the mutation leads to the continuous proliferation of cells due to the loss of GTPase activity (15,16). Moreover, a study by Li *et al* (9) showed 57.1% (28/49) of patients with CMA had KRAS mutations. In the present case report, the patient had no chronic inflammation, no genetic history, but did have microsatellite stability and MUC2-positive IHC. A KRAS p.G12d activating mutation was detected in the present case report, which aligns with the aforementioned literature findings on the CMA pathogenic mechanism involving MUC2 upregulation and KRAS mutation, and it is speculated that these two factors are the core pathogenic factors in this case.

KRAS mutation is an important target in the molecular mechanism of CRC, but the clinical value of different subtypes of mutations differs. Drug treatment regimens (sotorasib/adagrasib combined with cetuximab/panitumumab) have been recommended by the National Comprehensive Cancer Network (NCCN) guidelines for patients with CRC harboring KRAS p. G12c mutations (15). Although the KRAS p. G12d mutation has been detected in CRC (17), there is no approved drug for targeted therapy.

Diagnostic and typing value. The KRAS p. G12d mutation can be used as a molecular marker of PMA. Combined with MUC2 expression and other pathological features, it can help distinguish PMA from other perianal malignant tumors, such as sweat gland mucinous adenocarcinoma of skin and lung metastatic adenocarcinoma, especially for PMA cases without chronic inflammation. *Treatment direction*. Although no targeted drug is known, the presence of the KRAS p. G12d mutation provides a direction for subsequent treatment (preclinical trials are ongoing) (17).

Microscopically, the dysplastic glands within the tumor showed infiltrative growth, mucus lake formation and mild to severe glandular epithelial dysplasia (5). The typical immunohistochemical findings of non-anal gland, non-fistula associated mucinous adenocarcinomas suggest variable features: CK7(+), CK20(+) and CDX2(+) (8,11) or CK7(-), CK20 (+) and CDX2(+) (18). In the present case report, microscopically, the patient presented with expansive nodular growth with typical morphological changes of mucinous adenocarcinoma. Immunohistochemically, the patient was

positive for CK20, CDX2 and CK7, which was consistent with the results reported in the literature (7,10). Therefore, based on the medical history of the patient, H&E staining results and immunohistochemical findings, it is speculated that the tumor may have arisen from non-fistula-related glandular structures (acquired or congenital malformations or associated with embryonic residues) (8,16)

The differential diagnosis of PMA include the following: i) Infiltration or metastasis of CMA to the perianal tissue, such as the case reported by Spiridakiset *et al* (19), synchronous adenocarcinoma of the rectum and sigmoid colon implanted in the anal fistula, manifested as recurrent perianal abscess. However, colorectal adenocarcinoma immunohistochemical phenotype (CK7) is usually negative and can be distinguished; ii) mucinous adenocarcinoma derived from sweat glands of the skin is also rare, with prominent eosinophilic cytoplasm and positive expression of GCDFP-15 and no expression of CK20 and CDX2; and iii) gastrointestinal adenocarcinoma metastasis to the perianal region: A primary gastrointestinal tumor was excluded in the patient through colonoscopy and abdominal CT examination. Moreover, fistula or Crohn's disease was absent in the anorectal area. Therefore, the diagnosis of primary PMA was confirmed

There were prominent limitations in imaging evaluation in the present case report: The first B-ultrasound examination misjudged the hypoechoic mass as benign, and the anatomical relationship between the tumor and the anorectal part was not clear due to the lack of anal dual-plane ultrasound equipment (EAUS) and pelvic CT/MRI before the operation, which reflected that the doctor lacked clinical knowledge of PMA imaging examinations. Combined with previous studies and clinical practice, several preoperative imaging recommendations are proposed for suspected perianal masses.

Basic examination. EAUS is preferred for the diagnosis of perianal mass (7). EAUS can identify the 'multiple hypoechoic lesions' characteristic of mucinous tumors and can directly obtain pathological specimens through ultrasound-guided biopsy, notably reducing the rate of misdiagnosis (7,20). It is recommended as the first choice of imaging examination for suspected perianal masses (7), especially for cases of painless masses with clear boundaries. EAUS should be used to exclude the possibility of mucinous adenocarcinoma.

Advanced evaluation. Pelvic enhanced MRI and selective abdominal CT: Pelvic enhanced MRI has high resolution of soft tissue, which can accurately reveal the anatomical relationship between the tumor and anal canal, rectal wall and sphincter, determine the depth of tumor invasion and provide an important basis for establishing the scope of surgical resection (6). Abdominal and chest CT can assist in the detection of distant metastasis, such as liver and lung metastasis (21).

If imaging (EAUS/MRI) suggests mucinous adenocarcinoma features (such as mucinous lakes and invasive growth), ultrasound-guided biopsy should be performed immediately to avoid the possibility of accidentally ignoring malignancy due to 'benign imaging findings'. Even if the initial biopsy is negative, if PMA is still highly suspected (Such as perianal mass painless short-term enlargement), biopsy or immunohistochemical staining (such as CK7, CK20 and CDX2) should be performed again for further verification.

Future prospects of imaging examinations: i) Establish a standardized imaging examination process for perianal tumors. Compare the differences in diagnostic efficacy among B-ultrasound, EAUS, CT and MRI in the diagnosis of perianal tumors; ii) explore the combined diagnostic model of MRI and pathological examination. The combined diagnosis of 'MRI imaging features and puncture pathological results' improves the accuracy of preoperative examinations; and iii) conduct research on the optimization of individualized surgical plans under the guidance of MRI, further explore the application value of MRI in postoperative follow-up, provide a basis for precise postoperative follow-up and early intervention, and ultimately improve the long-term prognosis of patients.

In terms of treatment, a radical surgical approach, such as abdominoperineal resection and its variations, is often recommended in cases of late diagnosis or locally advanced tumors (11). Neoadjuvant chemoradiotherapy is recommended for locally advanced and metastatic diseases (7,22). NCCN guidelines recommend sotorasib/adagrasib combined with cetuximab/panitumumab for patients with CRC harboring KRAS p. G12c mutation (15). However, no drug targeting the KRAS p. G12d mutation has yet been approved for treating CRC (8). In terms of prognosis, according to the report by Gkegkes *et al* (7) among the 150 patients with PMA, 41 (29.3%) had recurrence, 32 (21.3%) had complications and 44 (29.3%) were deceased, while the rest were not clearly specified (7). In the present case, complete resection (R0) was achieved by radical local extended resection, which agreed with the treatment principles recommended by studies on early localized tumors (7,10). The patient had a clinical stage II tumor and did not need further adjuvant therapy after comprehensive analysis. No recurrence or metastasis was found after 12 months of follow-up, but regular follow-ups for local recurrence or distant metastasis are needed. Therefore conducting thoracic and abdominal contrast-enhanced CT scans plus MRI assessments every 3 months for the first 2 years postoperatively is recommended, followed by semi-annual (every 6 months) examinations for the subsequent 3 years and annual imaging evaluations thereafter for lifelong follow-up. The key point in the present case report is that the vigilance of presenting with a painless mass and no history of inflammation should be increased in clinical practice. EAUS is the preferred imaging modality for this assessment, and sole evaluation with conventional B-ultrasound should be avoided due to its limited spatial resolution and inability to accurately delineate the tumor's local extent, depth of invasion, and perirectal soft tissue involvement. Multiple sampling can avoid the missed diagnosis of a single biopsy. The nature of the tumor can be determined by examining frozen sections during the operation.

In conclusion, PMA is relatively rare in clinical practice and occurs in various forms. The present case was unique as the tumor had a rapid growth rate and an uncommon KRAS p. G12d mutant subtype was identified through genetic testing. An accurate diagnosis before the operation is difficult. For painless PMA, a comprehensive diagnosis should be performed by combining clinical, pathological, immunohistochemical, genetic testing and imaging methods. Early and accurate

diagnosis enables patients to receive timely and appropriate treatment, which can help avoid missed diagnoses and delayed treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The data generated in the present study may be found in the Genome Sequence Archive for Human under accession number HRA014514 or at the following URL: https://ngdc.cncb.ac.cn/gsa-human/browse/HRA014514.

Author's contributions

JS and JY drafted the manuscript and conceived the study. JS and GL were responsible for the collection and analysis of case data and literature. JY, XW, YZ and JS revised the manuscript and interpreted the data. JS, XW and GL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Ethical consent was provided by the Ethics Committee of The First People's Hospital of Xiaoshan (approval no. 2024-12).

Patient consent for publication

Before the research was carried out, the patients and their families were fully informed of the research purpose of this case report, the scope of data use and the form of publication. The patients and their families voluntarily signed the written informed consent form, agreeing to use their clinical data, pathological and molecular testing data for the writing and public release of this case report. All data were anonymized to protect the privacy of the patients.

Competing interests

The authors declare that they have no competing interests.

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