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CASE REPORT

POLE-Mutant Colon Adenocarcinoma—Case Presentation and Histopathological Evaluation

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Abstract

Introduction *POLE* mutant phenotype in colon adenocarcinomas represents a rare molecular subtype. These tumours are generally responsive to immune-checkpoint inhibition therapy and, therefore, are currently considered as a subtype with good prognosis. We hereby present the first detailed case presentation of a *POLE* mutant colon adenocarcinoma with useful microscopic features.

Case Report A 53-year-old male patient's colon adenocarcinoma histologically showed wide variety of growth patterns and massive intra- and peritumoural lymphocytic infiltrate. The majority of the tumour consisted of a high-grade component resembling medullary carcinoma of the colon, while approximately one-third of the tumour was composed of conventional areas exhibiting a tubular pattern. A minority of the tumour was constituted by poorly cohesive rhabdoid cells. Immunohistochemistry was performed, and colorectal origin was proven with CDX-2 and SATB2. Furthermore, proficiency in mismatch repair proteins and SMARCB1 deficiency was observed. The unusually high-grade colon adenocarcinoma, with areas mimicking medullary carcinoma, and generally aggressive morphology raised suspicion of microsatellite instability. The diverse morphology and the SMARCB1 deficiency also raised suspicion of ultramutation caused by POLE alteration. Next-generation sequencing panel confirmed a pathogenetic mutation in *POLE* exon 9: p.Pro286Arg, c.857C > G.

Discussion The diverse, high-grade morphology and increased intratumoural lymphoid infiltration should raise suspicion for *POLE*-mutated adenocarcinoma during everyday histopathological practice. Mismatch repair proficiency results on immunohistochemistry should not determine the final diagnosis, as only a minor percentage of these tumours are MSI. In every case suspicious for *POLE*-mutated adenocarcinoma, a 500-cancer gene panel should be carried out.

Keywords POLE mutation · POLE-mutant colon adenocarcinoma · Immune-checkpoint inhibition therapy · Next-generation sequencing

Abbreviations

CDX-2	Caudal-type homeobox transcription factor 2
CT	Computed tomography
DNA	Deoxyribonucleic acid
EMA	Epithelial membrane antigen
INI1	Integrase interactor 1
MLH1	MutL protein homolog 1
MMR	Mismatch repair
MSH2	MutS homolog 2
MSH6	MutS homolog 6
MSI	Microsatellite instability
MSS	Microsatellite stable
NGS	Next-generation sequencing
PMS2	PMS1 Homolog 2
POLD1	DNA polymerase delta 1 catalytic subunit
POLE	DNA polymerase epsilon
SATB1	Special AT-rich sequence-binding protein 2
SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4
SMARCB1	Switch/Sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1
TMB	Tumour mutation burden

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Introduction

According to the current World Health Organisation (WHO) Classification of tumours of the Digestive System, DNA polymerase epsilon (*POLE*) mutant phenotype in colon adenocarcinomas represents a rare molecular subtype (3%) [1, 2]. These tumours generally have a high tumour mutation burden (TMB), while ultramutation results in an increase in neoantigen expression. These tumours with high neoantigen levels are generally responsive to immune-checkpoint inhibition therapy; therefore, *POLE*-mutant colon adenocarcinomas are currently considered as a subtype with good prognosis [2, 3]. As a thorough literature research did not reveal any detailed previous case reports on the histology of these tumours, we consider our case the first detailed case presentation of a *POLE* mutant colon adenocarcinoma with useful microscopic features.

Case Report

A 53-year-old male patient was admitted to hospital for examination due to abdominal cramps and hematochezia. His medical history did not include any significant diseases. Colonoscopic examination revealed an obliterating tumour at the lienal flexure. Due to the obstruction, primary surgical treatment was recommended. At the macroscopic examination of the surgical specimen, the tumour measured 6 cm in its largest diameter, and infiltration of the serosal surface was also visible. Histologically, 2 of the most remarkable features were a wide variety of growth patterns and massive intra- and peritumoural lymphocytic infiltrate with formation of tertiary lymphoid structures. The majority of the tumour consisted of a high-grade component resembling medullary carcinoma of the colon, while approximately one-third of the tumour was composed of conventional areas exhibiting a tubular pattern with the well known "tall, dark, and dirty" appearance (Fig. 1a, b). A minority of the tumour was constituted by poorly cohesive rhabdoid cells (Fig. 1c). In all areas, the tumour cells exhibited uniform nuclear structure with vesicular chromatin and prominent, central, cherry-red nucleoli. An expansive infiltration front was observed, along with venous and lymphatic spread. At the tumour's edge, a polypoid, focally serrated, in situ lesion was present with highly atypical cells similar to the cells observed in the invasive component (Fig. 1d). Colorectal origin was confirmed by CDX-2 and SATB2 immunohistochemical stainings (Fig. 1e, f). Focal cytoplasmic positivity was observed with villin (Fig. 1g). Further immunohistochemistry revealed proficiency in MLH1, MSH2, MSH6, and PMS2 mismatch repair proteins (pMMR), but aberrant loss of switch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1). SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 (SMARCA4) expression was partially lost (Fig. 1h, i). Epithelial membrane antigen (EMA) showed diffuse membranous positivity (not shown).

The unusually high-grade colon adenocarcinoma, with areas mimicking medullary carcinoma, and generally aggressive morphology raised suspicion of microsatellite instability (MSI). Even though MMR proficiency was observed on immunohistochemical examination, it must be emphasized that it does not exclude the possibility of MSI. The diverse morphology and the SMARCB1 deficiency also raised suspicion of ultramutation caused by POLE alteration; therefore, molecular examination was performed. Next-generation sequencing (NGS) panel (Oncomine Comprehensive Assay Plus Panel, Thermo Fisher) confirmed a pathogenetic mutation in *POLE* exon 9: p.Pro286Arg, c.857C > G, and a high TMB (112.07). The tumour proved to be microsatellite stable (MSS) with NGS, as well.

After the surgery, the patient received capecitabine-oxaliplatin chemotherapy, and the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab. The computed tomography (CT) did not reveal any metastases. After 4 months of follow-up, the patient shows no residual or metastatic disease despite the high-grade histomorphology and the advanced local tumour stage.

Discussion

Colorectal adenocarcinoma remains one of the most common cancers in both genders, with generally poor prognosis, due to the fact that a quarter of the patients already present with metastatic disease at the time of diagnosis [4]. In individuals under the age of 50, it represents the most common cause of cancer-related death in men [5]. Biologically, colorectal adenocarcinoma represents a tumour with numerous heterogeneous subtypes and many already identified prognostic factors [4].

Mutations in the proofreading exonuclease domains of DNA polymerase genes, DNA polymerase delta 1 catalytic subunit (*POLD1*), and *POLE* lead to impaired proofreading function and, therefore, an extremely high TMB with more than a hundred point mutations per megabase in tumour cells. The consequence of this unique genotype is a variegated histologic picture and frequent subclonal mutational pattern with the immunohistochemically applied tumour suppressor (p53, SMARCB1, and SMARCA4) and mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6). Another sequel is the expression of many altered immunologically foreign proteins on the surface of the tumour cells, which leads to a massive lymphoid cell infiltration and effective tumour cell destruction. Thus, despite the usually

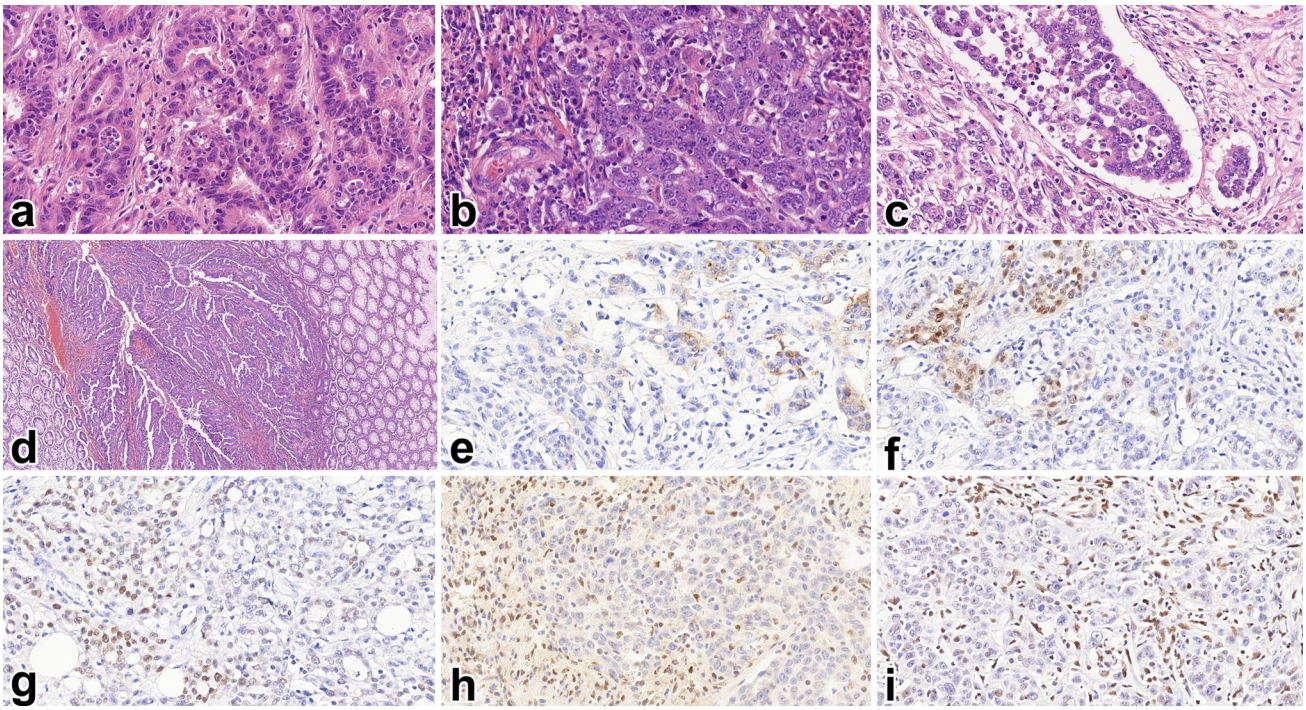

Fig. 1 Morphological characteristics and immunohistochemical profile of *POLE* mutant adenocarcinoma. **a** Conventional tubular area in a *POLE* mutant colorectal adenocarcinoma with the well-known "tall, dark and dirty" appearance (HE, 40x). **b** An area mimicking medullary carcinoma of the colon. The high-grade tumour cells form syntitial sheets and cords with an adjoining brisk lymphocytic infiltration (HE, 40x). **c** Loosely cohesive rhabdoid cells showing infiltration of the stroma and lymphovascular invasion (HE, 40x). **d** In situ neoplasm on the edge of the invasive tumour. High-grade tumour cells form an exophytic, papillary, and partly serrated lesion (HE, 5x). **e** Immunohistochemistry for villin shows scarce, faintly positive tumour cells (Villin, 40x). **f** CDX2 antibody decorates scattered nuclei of tumour cells (CDX2, 40x). **g** SATB2 shows a partial positivity in tumour cells in a similar pattern as the CDX2 (SATB2, 40x). **h** SMARCA4 shows loss of expression in the tumour cells (SMARCA4, 40x). **i** SMARCB1 shows variable loss in the neoplastic cells (SMARCB1, 40x). CDX-2: caudal-type homeobox transcription factor 2; HE: hematoxylin and eosin; POLE: DNA polymerase epsilon; SATB2: special AT-rich sequence-binding protein 2; SMARCA4: SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; SMARCB1: Switch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1

high-grade histological picture, these tumours have good prognosis even at an advanced local tumour stage [6].

POLE plays an essential role in the DNA proofreading mechanism, by lengthening the leading strand [2, 4]. Somatic mutations of *POLE* are observed in 3% of all colorectal adenocarcinoma cases; however, proofreading domain mutations are even less frequent (1–2%) [1, 7]. *POLE* mutation in familial colon adenocarcinoma cases is extremely rare; so far, only few families have been described with this mutation. *POLE* mutation does not predispose for colon adenomas and carcinomas, and carriers are prone to develop pancreatic, small intestinal, ovarian, endometrial, and brain tumours, as well [8–10].

While currently, only MSI cancers are prone to receive immunotherapy, the identification of *POLE* mutation is essential. Similar to their endometrial counterpart, *POLE*-mutated colorectal adenocarcinoma represents a good prognostic subtype [2, 3, 7]. The reason for this may lie in the fact that the overproduction of neoantigens may induce a cytotoxic T-cell response [2, 7]. According to the results of Bikhcandani et al., clearance of circulating DNA is a possible result of immunotherapy in *POLE* mutant adenocarcinomas [5]. These tumours represent a rare subtype; therefore, the examination of ultramutation caused by *POLE* alteration is not a part of routine pathological diagnostics. According to the results of Hu et al., these tumours are often observed in younger patients (< 50 years), and there is a definitive male predominance. In the Asian population, left-sided colon predominance was observed, while in the non-Asian population, right colon predominance was seen [2].

Hereby, we presented the first histologically well-documented case of *POLE*-mutated adenocarcinoma, along with essential microscopic photographs. The diverse, high-grade morphology and increased intratumoural lymphoid infiltration (≥ 4 lymphocytes per high-power field) should raise suspicion for *POLE*-mutated adenocarcinoma during everyday histopathological practice [11, 12]. MMR proficiency results on immunohistochemistry should not

determine the final diagnosis, as only a minor percentage of these tumours are MSI [7]. In every case suspicious for *POLE*-mutated adenocarcinoma, a 500-cancer gene panel should be carried out, capable of confirming the ultramutated status and the *POLE* mutation itself. Despite the histologically aggressive morphology, including the often observed higher grade and stage, the identification of *POLE* mutation is essential, as the consequent strong response to immunotherapy generally results in a good prognosis [2, 3]. Furthermore, carriers of *POLE* mutations are predisposed to other, extraintestinal tumours, as well [8, 9].

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Declarations

Consent Informed consent to participate and to publish was obtained from the patient.

Competing Interest The authors declare no competing interests.

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