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Novel Insights from Research Practice

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Colonic Tubular Adenoma with Clear Cell Change: Case Report with Whole-Exome Sequencing and Updated Review of the Literature

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Established Facts

- Colorectal tubular adenomas displaying clear cell change are rare entities, with unknown clinical relevance, prognosis, immunohistochemical, and molecular features.
- Solely 22 cases have been reported in the literature.
- Whole-exome sequencing has not been carried out.
- Hitherto, neither special stainings nor immunohistochemical markers proved to be useful in the diagnostic process.

Novel Insights

- Hereby we report a case of a 43-year-old female patient with a rectosigmoid polyp. Whole-exome sequencing (WES) was carried out and revealed high tumour mutation burden and 7 pathogenic mutations, including TP53, APC, FGFR4, EHBP1, IL4R, TYR, and ACTN3.
- Our WES resulted in newly found pathogenic mutations, and high mutation burden, proving the lesion's neoplastic origin.
- From a differential diagnostic perspective, enteroblastic differentiation, primary and secondary clear cell adenocarcinoma has to be excluded.

Keywords
Colon adenoma · Clear cell change · Whole-exome sequencing

Abstract
Introduction: Colorectal tubular adenomas displaying clear cell change are rare entities, with unknown clinical relevance, prognosis, immunohistochemical, and molecular features. ***Case Presentation:*** Hereby we report a case of a 43-year-old female patient with a rectosigmoid polyp. Histologically,

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conventional dysplasia was visible with scattered areas displaying clear cell change. Whole-exome sequencing (WES) was carried out and revealed high tumour mutation burden and 7 pathogenic mutations, including *TP53, APC, FGFR4, EHBP1, IL4R, TYR,* and *ACTN3*. ***Conclusion:*** Clear cell change may only be present in less than 0.1% of adenomas. Aetiology is not well understood; additionally, few authors suggest autolysis or fixation problems. Our WES resulted in newly found pathogenic mutations, and high mutation burden, proving the lesion's neoplastic origin. Hitherto, neither special stainings nor immunohistochemical markers proved to be useful in the diagnostic process. From a differential diagnostic perspective, enteroblastic differentiation, primary and secondary clear cell adenocarcinoma has to be excluded.

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Introduction

Colon adenoma with clear cell change (CCC) is a rare finding that has been first observed in 1983 by Reed et al. and first properly detailed in 1998 by Suzuki et al. [1, 2]. Since then, solely 22 cases have been reported in the literature. In 2 cases, conventional or clear cell adenocarcinoma (CCA) components have been described, as well [3, 4]. CCC is rare; therefore, biological behaviour is currently unknown. To determine the specific immunophenotype, molecular alterations, or clinical significance, further information is needed. We report a case of tubular adenoma (TA) with CCC and provide an updated literature review, as well.

Case Report

A 43-year-old female patient with a medical history of systemic lupus erythematosus underwent colonoscopic examination due to hematochezia. From the rectosigmoid region, a 15 mm polyp was resected.

Histologically, predominantly clear cells (>80%) with vacuolated cytoplasm were visible, with sparse epithelial cells resembling "conventional" dysplasia (Fig. 1a, b). Eventually, signet ring cell morphology was present, as well (Fig. 1c). Periodic acid-Schiff (PAS) and Alcian blue (AB) staining remained negative in these areas. Immunohistochemical (IHC) examination was performed, p53 reflected mutant phenotype (Fig. 1d), while glypican 3, Sal-like protein 4 (SALL4), Alpha fetoprotein (AFP), and Cluster of differentiation 10 (CD10) were negative. Ki67 showed similar results

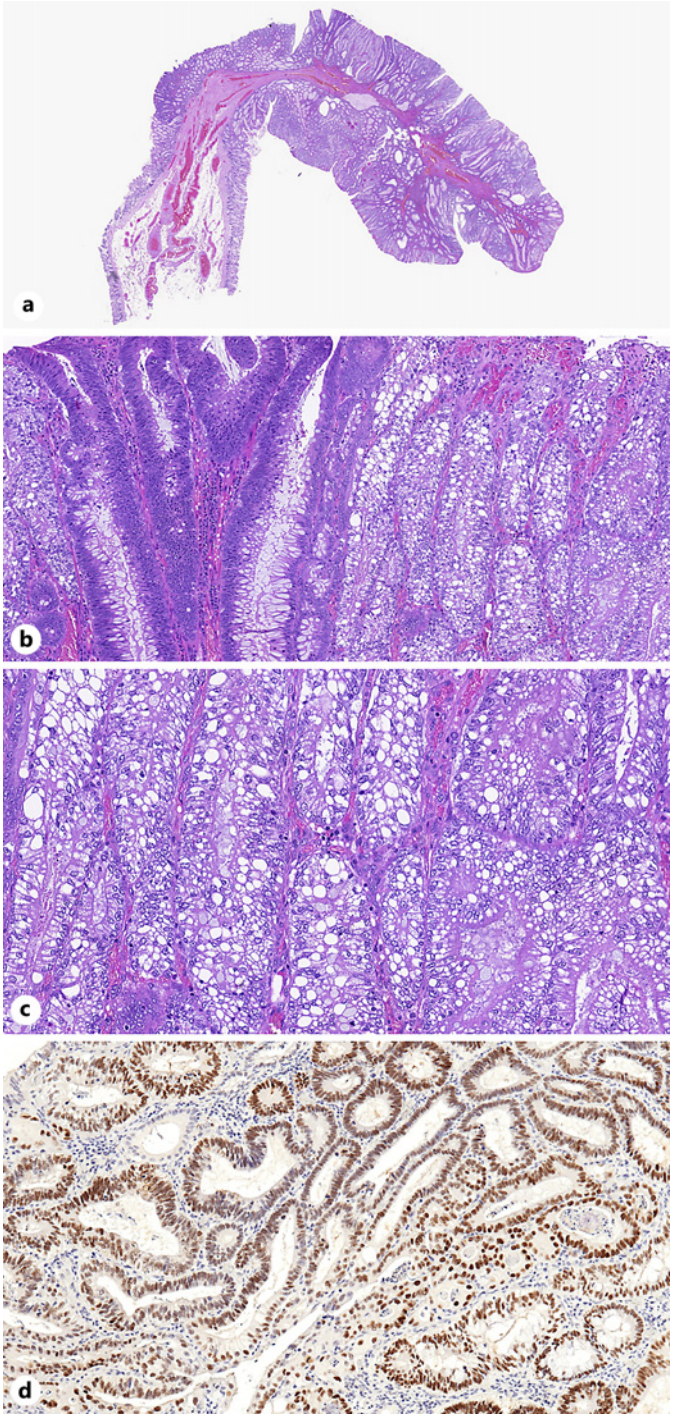

Fig. 1. Microscopic finding of the rectosigmoid polyp. **a** Pedunculated polyp composed of tubular structures (HE. ×1). **b** Low-grade conventional dysplasia and CCC was visible in a patchy manner (HE. ×10). **c** Clear cells were visible with vacuolated cytoplasm and eventually signet ring cell morphology (HE. ×15). **d** Mutant phenotype was observed with p53 (p53. ×10). HE, hematoxylin and eosin staining.

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Table 1. Summary of pathogenic and likely pathogenic mutations found in our case

Gene	Variant allele frequency, %	ClinVar significance	Coding impact
TP53	8.4	Pathogenic	Missense
APC	17.2	Pathogenic	Nonsense
FGFR4	44.3	Pathogenic	Missense
EHBP1	27.5	Pathogenic	Splice site variant
IL4R	48.8	Pathogenic	Missense
TYR	47.6	Pathogenic	Missense
ACTN3	43.4	Pathogenic	Nonsense
PDX1	42.3	Likely pathogenic	Missense

ACTN3, alpha actin 3; APC, adenomatous polyposis coli; EHBP1, EH domain binding protein 1; FGFR4, fibroblast growth factor receptor 1; IL4R, interleukin 4 receptor; PDX1, pancreatic and duodenal homeobox 1; TP53, tumour protein p53; TYR, tyrosinase.

in the conventional dysplastic and the clear cell areas. Invasion was not visible. The case was concluded as TA with CCC.

Ten serial sections of 10-µm thickness per formalin-fixed, paraffin-embedded sample were taken, and deoxyribonucleic acid (DNA) was extracted. DNA concentration was measured by Quant-iT 1x dsDNA HS Assay kit (Thermo Fisher Scientific) with FLUOstar Omega (BMG Labtech) plate reader. For whole-exome sequencing (WES) library construction, Twist Library Preparation EF Kit 2.0 with Universal Adaptor System and Exome 2.0 Panel (Twist Bioscience) was applied. The fragment size distribution of the precapture and postcapture libraries was determined by capillary electrophoresis on LabChip GX Touch HT Nucleic Acid Analyzer by using X-Mark HT Chip and DNA NGS 3K Assay kit (PerkinElmer). The libraries were quantified by Quant-iT 1x dsDNA HS Assay kit (Thermo Fisher Scientific) with FLUOstar Omega (BMG Labtech). In average, more than 24 Gbp raw data were generated from the sample; demultiplexing, adapter trimming, Q30 filtering, and somatic variant calling of the sequenced data were performed on Dragen Bio-IT platform (Illumina). Genomic variants of Vcf files were annotated by using the Nirvana Software package.

Altogether 7 pathogenic mutations were identified, including *tumour protein p53 (TP53), adenomatous polyposis coli (APC), fibroblast growth factor receptor 1 (FGFR4), EH domain binding protein 1 (EHBP1), interleukin 4 receptor (IL4R), tyrosinase (TYR)*, and *alpha actin 3 (ACTN3). Pancreatic and duodenal homeobox 1 (PDX1)* was interpreted as likely pathogenic. All pathogenic and likely pathogenic mutations are listed in Table 1. Tumour mutation burden proved to be 17.76, demonstrating the lesion's true neoplastic nature and disproving the earlier assumptions regarding its potentially iatrogenic or autolytic origin.

Discussion with Updated Review of the Literature

The presence of clear cell morphology, whether observed in adenoma or carcinoma, falls under the category of "unconventional" and rare differentiations in colonic neoplasms. According to the current World Health Organization's Classification of Digestive System Tumours, they are present in less than 0.1% of adenomas [5]. Currently, there are 10 publications in the literature regarding CCC in colorectal adenomas, including 22 cases. During our search for literature, keywords of "colon," "adenoma," "CCC," "clear cell metaplasia," and "clear cell component" were applied. CCC in TA was first properly described by Suzuki et al. [2] in 1998, characterized by tubular glands consisting of clear cells with moderate to severe atypia and vacuolated cytoplasm. PAS and AB were negative. With IHC examination, the clear cell component was positive for carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA). P53 did not reveal either mutant or null phenotype; however, elevated proliferation index was observed with Ki67. No codon 12 mutation was present in the c-K-ras gene with polymerase chain reaction. Based on the immunoprofile, the authors concluded that CCC has no association towards malignant progression in the adenoma-carcinoma sequence [2].

At the time of writing this publication, 3 literature reviews exist on CCC in colorectal adenomas [3, 6, 7]. Domoto et al. [6] work from 1999 includes 4 publications and their own data. The work of Chan et al. [7] comprises the data of 9 publications and was presented in 2014. The latest one is from Oyama et al. from 2019, detailing 8 publications [3]. Table 2 presents all articles discussing colonic adenomas with CCC. The first publication with coloured microphotos was published in 2008 by Pusztaszeri and Bouzourene [8]. Regarding the limitations of the articles, the work of Shi et al. [9] does not include all gender and age data of all patients; therefore, they are missing from Table 2.

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Table 2. Summary of literature review regarding colon adenoma with CCC

Author and year of publication	Case number (*n*)	Gender	Age	Aetiology/ iatrogenic effect	Localization	Increased mitotic activity	Result of special staining, if applicable	Result of molecular examination, if applicable	Association with clear cell colon adenocarcinoma
Suzuki et al. [2] (1998)	1	m	62	NA	Descending colon	NA	PAS negative, AB negative	*c-K-ras* wildtype	NA
Domoto et al. [6] (1999)	3	3 m	54; 45; 44	NA	Sigmoid colon; transverse colon; sigmoid colon	Present	PAS negative, scattered positivity with AB in all cases	NA	NA
Pusztaszeri et al. [8] (2008)	1	m	62	NA	Sigmoid colon	Present	PAS negative, PAS-D negative, AB negative	NA	NA
Eloy et al. [10] (2009)	3	m, f, f	68; 84; 48	NA	Sigmoid colon; sigmoid colon; transverse colon	NA	PAS negative, PAS-D negative in all cases, AB negative in all cases	NA	NA
Shi et al. [9] (2010)	9	3 m, 3 f, 3 NA	61; NA; 63; 63; 68; 30; 35	NA	Sigmoid colon; NA; ascending colon; rectum; NA; sigmoid colon; sigmoid colon	NA	PAS negative in 4 cases, PAS-D negative in 4 cases	NA	NA
Chan et al. [7] (2014)	1	f	75	NA	Ascending colon	NA	PAS negative, AB negative	NA	NA
Yao et al. [11] (2016)	1	m	48	NA	Sigmoid colon	NA	PAS negative, AB negative	NA	NA
Miyasaka et al. [12] (2018)	1	m	63	NA	Ascending colon	NA	PAS negative, PAS-D negative, AB negative	NA	NA

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Table 2 (continued)

Author and year of publication	Case number (*n*)	Gender	Age	Aetiology/ iatrogenic effect	Localization	Increased mitotic activity	Result of special staining, if applicable	Result of molecular examination, if applicable	Association with clear cell colon adenocarcinoma
Oyama et al. [3] (2019)	1	m	75	NA	Rectum	NA	PAS negative, PAS-D negative, AB negative	NA	NA
Tochio et al. [4] (2021)	1	m	57	NA	Transverse colon	NA	PAS negative, AB negative	NA	Present
Our case, 2023	1	f	43	Suspicion for autolysis	Rectosigmoid region	NA	PAS negative	*TP53, APC, FGFR4, EHB1, IL4R, TYR, ACTN3, PDX1*	NA

AB, Alcian blue; ACTN3, alpha actin 3; APC, adenomatous polyposis coli; c-K-ras, c-Kirsten rat sarcoma virus; PAS-D, periodic acid-Schiff plus diastase; EHBP1, EH domain binding protein 1; FGFR4, fibroblast growth factor receptor 1; IL4R, interleukin 4 receptor; PAS, Periodic acid-Schiff; PDX1, pancreatic and duodenal homeobox 1; TP53, tumour protein p53; TYR, tyrosinase; m, male; f, female.

Based on the currently available information, aetiology is doubtful. Some publications mention autolysis or carbohydrate elution during processing or fixation, but electron microscopy has yet to confirm any of these possibilities [3, 6, 8]. Lipid accumulation or hydropic change has been suggested, as well. Therefore, it has not yet been decided whether the lesion is truly neoplastic or metaplastic [13].

Patients are middle aged, with an average of 57 years (range: 30–84). Male predominance can be observed with male:female ratio of 13:6 (in 3 cases, gender is unknown). Three articles mention the patient being Japanese; however, it has to be emphasized that the majority of literature is from this country [2, 4, 11, 12]. Generally, the lesions occur in the left colon, including in order of occurrence: sigmoid colon (n = 9), rectum (n = 2), and descending colon (n = 1). Multiplicity was described in a single case by Miyasaka et al. [12].

Regarding microscopic findings, all articles describe corresponding morphology, localized to the superficial part of adenomas, with the clear cells in accordance with enterocytes, and morphology is caused by clear, vacuolated, or foamy cytoplasm [13]. The already examined special stainings and IHC markers differ. While CCC has no mucin accumulation, PAS and PAS-D remained negative in all cases [13]. Solely scattered positivity was observed with AB in the 3 cases described by Domoto et al. [6]. Increased mitotic activity was mentioned by Domoto et al. and Pusztaszeri and Bouzourene [6, 8]. Ki67 or mind bomb 1 (MIB1) was carried out in 9 cases, with highly variable results (range: 8–73.7%).

A unified IHC profile has not yet been identified. Carcinoembryonic antigen (CEA), cytokeratin 20 (CK20) proved to be positive in all cases examined. Caudal-type homeobox transcription factor 2 (CDX2) was positive in all investigated cases, except for a single one [9]. Mucin 5AC (MUC5AC), Mucin 6 (MUC6), SALL4, vimentin, chromogranin, and AFP were negative in all examined cases [3, 4, 7–10, 12]. Online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000538705) highlights the immunoprofile of every lesion included in published literature, featuring ours.

Electron microscopic examination was carried out in a single case, revealing the substance of CCC to be of lipid nature [10]. Molecular examination was carried out in the first case; however, pathogenic mutation has not been identified yet [2]. CCC has been observed alongside conventional TAs in both low- and high-grade dysplastic

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settings, and one single case described association with early CCA [4].

Regarding differential diagnosis, CCA has been described before; however, it has to be emphasized that it is not yet identified as a separate subtype [5, 14]. In each case, the possibility of metastases has to be excluded, including clear cell renal cell carcinoma and CCA of the ovary. CCC also has to be differentiated from enteroblastic differentiation due to similar microscopic morphology. In this case, glypican 3, SALL4, and AFP IHC markers may be helpful. Currently, the prognostic value of CCC is not known [4].

Hereby, we reported a case of a 43-year-old female patient with TA, presenting CCC. Specific special stainings or IHC markers were not identified. WES proved the lesion's neoplastic origin. Several pathogenic and likely pathogenic mutations were found, including *TP53, APC, FGFR4, EHBP1, IL4R, TYR, ACTN3,* and *PDX1.*

The role of *TP53* and *APC* mutations in colon adenomas and carcinomas has been widely known and accepted [5, 15]. *FGFR4* has been examined in colon adenomas solely by Wang et al.; however, it has been associated with advanced stage and high metastatic potential in colorectal adenocarcinomas [16, 17]. The remaining found genetic mutations in our case have not been so far associated with colon adenomas. *EHBP1*, *IL4R*, and *ACTN3* have been described in connection with colorectal adenocarcinomas [18–20]. Currently, there is only one research in the literature regarding *PDX1* and its connection to colorectal adenocarcinomas, with uncertain results. According to Ballian et al. [21], *PDX1* was scarcely detected in normal, tumour-free tissue, while low levels were revealed in primary tumours, and high levels were seen in metastatic setting, altogether raising suspicion that *PDX1* may be a potential tumour marker. *TYR* so far has been associated with atypical teratoid/rhabdoid tumours [22].

The genetic background of conventional TAs has been studied in recent years, and so far mainly *TP53, APC, Kirsten rat sarcoma (KRAS), V-Raf murine sarcoma viral oncogene homolog B (BRAF), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA),* and *telomerase reverse transcriptase (TERT)* mutations have been identified [23]. CCC remains a rare lesion of colorectal adenomas, with unknown aetiology and prognostic significance. Hereby, we presented a case with similar clinical features to earlier case presentations with WES and an updated literature review including results of special staining, IHC markers, electron microscopy, and molecular analysis.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This study protocol was reviewed and approved by institutional Ethical Committee of the Albert Szent-Györgyi Clinical Centre of the University of Szeged (4988).

Conflict of Interest Statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Author Contributions

Data collection: Ádám Ferenczi, Anita Sejben, and István Sejben; interpretation of the results of whole-exome sequencing: Levente Kuthi and Anita Sejben; conceptualization and funding acquisition: Anita Sejben; writing: Ádám Ferenczi and Anita Sejben; and review and editing: Ádám Ferenczi, Levente Kuthi, István Sejben, and Anita Sejben.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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