

Certificate of Attendance

We hereby confirm the participation at the:

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Introduction: Colorectal tubular adenomas displaying clear cell change are rare entities, with unknown clinical relevance, prognosis, immunohistochemical, and molecular features. So far, solely 22 cases have been reported in the literature, and whole exome sequencing (WES) has never been carried out before.

Case report: Hereby, we report a case of a 43-year-old female patient, who underwent colonoscopy due to hematochezia. During the examination, a rectosigmoid polyp was found. Histologically, conventional dysplasia was visible with scattered areas displaying clear cell change. Immunohistochemical examination was performed, and Glypican 3, SALL4, AFP, and CD10 were negative. WES was carried out revealing high tumour mutation burden (17.76 mut/Mb) and seven pathogenic mutations, including *TP53*, *APC*, *FGFR4*, *EHBP1*, *IL4R*, *TYR*, and *ACTN3*.

Discussion: Clear cell change may only be present in less than 0.1% of adenomas, according to the current World Health Organisation's Classification of Digestive System Tumours. Etiology 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, and disproving the earlier assumptions regarding its potentially iatrogenic or autolytic 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 in each case.

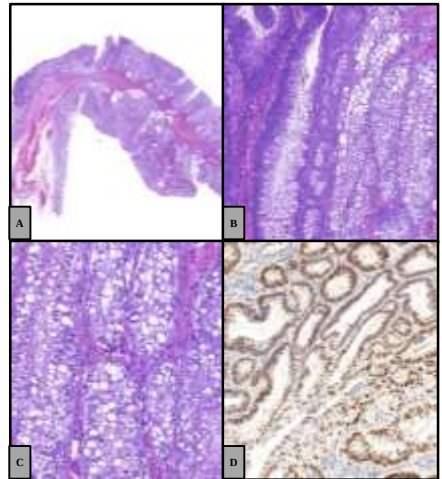


Figure 1 Microscopic finding of the rectosigmoid polyp. A: Pedunculated polyp composed of tubular structures (HE, 1x). B: Low-grade conventional dysplasia and clear cell change was visible in a patchy manner (HE, 10x). C: Clear cells were visible with vacuolated cytoplasm, and eventually, signet ring cell morphology (HE, 15x). D: Mutant phenotype was observed with p53 (p53, 10x).

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

Table 1 Summary of pathogenic and likely pathogenic mutations found in our case (ACTN3 - Alpha actin 3; APC - Adenomatous polyposis coli; EHBP1 - EH domain binding protein 1; FGFR4 - Fibroblast growth factor receptor 4; IL4R - Interleukin 4 receptor; PDX1 - Pancreatic and duodenal homeobox 1; TP53 - Tumour protein p53; TYR - Tyrosinase)

