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Is it time to acknowledge intramucosal colorectal carcinoma?

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Is it time to acknowledge intramucosal colorectal carcinoma?

Aim: The term 'intramucosal carcinoma' in the colorectum is controversial when used as a synonym for high-grade dysplasia. However, setting clear definitions for this diagnosis (i.e. *unequivocal infiltrative growth in the lamina propria, which might be most easily recognized in cases with overt poor differentiation or formation of signet ring cells or tumour budding*) allow us to investigate its relevance.

Methods and Results: We reviewed cases from our archive (1990–2024) and selected 14 true intramucosal carcinomas using our strict histological criteria, excluding high-grade dysplasia and invasive carcinomas. These occur primarily in conventional adenomas and are frequently associated with microsatellite instability (50%). Our study shows a low estimated incidence of intramucosal carcinoma (0.01%) in population screening and highlights the low lymph node risk and the good outcome of patients with intramucosal carcinoma.

Conclusion: The rare diagnosis of intramucosal colorectal carcinoma aids in identifying patients at increased colorectal cancer risk, notably those with hereditary syndromes. Standardizing this diagnosis is critical to prevent overdiagnosis and unnecessary treatment.

Keywords: colorectal cancer, intramucosal carcinoma, mismatch repair deficiency

Introduction

In contrast to carcinomas arising elsewhere in the tubular gut, the diagnosis of intramucosal carcinoma of the colorectum is controversial. This term is sometimes used as a synonym for high-grade dysplasia (HGD), which causes overdiagnoses, resulting in 'undue alarm' for both patients and clinicians.[1] On the other hand, diagnosing HGD instead of intramucosal carcinoma may lead to underdiagnosis and undertreatment. In the Japanese literature, intramucosal colorectal carcinoma (CRC) is more frequently reported, since CRC is diagnosed independently of invasion depth in the Japanese classification system.[2,3]

The main argument for putting intramucosal carcinoma in the group of high-grade adenomas is their very low risk of lymph node metastases. Initially, it was believed that—in contrast to gastric mucosa—

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Abbreviations: CRC, colorectal carcinoma; dMMR, mismatch repair deficient; F, female; HGD, high grade dysplasia; IBD, inflammatory bowel disease; IEL, intraepithelial lymphocytosis; M, male; MMR, mismatch repair; NA, not assessable; NED, no evidence of disease; pMMR, mismatch repair proficient; SRC, signet ring cells; SSL, sessile serrated lesion; TA, tubular adenoma; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma.

lymphatics above the level of the muscularis mucosae were lacking.[4] However, with the use of specific antibodies for lymphatics, it became clear that there are indeed lymphatics in the mucosa,[5–7] challenging this dogma.[8] Literature about the actual lymph node risk of intramucosal carcinoma is scarce and unreliable. Data from cancer registries[9] showed positive lymph nodes in up to 4.6% of cases; however, no pathology review was included. It seems that in these series the initial biopsy diagnosis of intramucosal CRC was not adapted after resection, which was likely invasive in most cases.[10] Indeed, other series showed no lymph node metastases in 55 and 118 cases.[11,12]

Due to the introduction of population screening in many countries,[13] combined with improved endoscopic techniques, there might be an increase in the number of detected intramucosal carcinomas, in line with the increase of pT1 CRC.[14] This offers the possibility to investigate whether the introduction of intramucosal CRC diagnosis helps to improve patient care. Small series in the literature[15] suggest that the outcome of these patients is in general good, although cases with a poor outcome have occasionally been described.[16] However, potentially different outcomes should not be the only reason for distinguishing intramucosal CRC from HGD in the diagnostic workup of colorectal neoplasia. Detection of patients with a high risk for CRC development, either sporadic, associated with inflammatory bowel disease, or hereditary syndromes, is important for effective surveillance. It has been suggested that, indeed, intramucosal carcinoma occurs more frequently in these patient groups[17–19] and might, therefore, be an indicator facilitating the identification of high-risk patients.

In the current study, we collected a cohort of intramucosal carcinomas, re-reviewed the histology and explored their associations with intestinal comorbidities such as inflammatory bowel disease (IBD) and hereditary cancer, specifically Lynch syndrome.

Materials and methods

COHORT SELECTION

In the local archive of the Department of Pathology, Radboudumc, Nijmegen, we searched for intramucosal colorectal carcinomas diagnosed between 1990 and 2024, using three different search terms: 'intramucosal carcinoma', 'carcinoma *in situ*', and 'intramucosal signet ring cells'. All cases were reviewed by two independent pathologists (I.D.N., R.Svd.P.) and a physician assistant certified in gastrointestinal histopathology (MEV-B). Biopsies were excluded. High-grade dysplasia (characterized as atypical epithelial proliferation without disruption of the basal membrane) and cases with invasive carcinoma (in subsequent resections) were excluded. To diagnose intramucosal carcinoma, the atypical epithelial proliferation was limited to the mucosa and clear disruption of the basal membrane was present, with evident intramucosal budding and/or formation of signet ring cells. To estimate the relative incidence of intramucosal carcinomas, we determined the number of patients with (high-grade) dysplasia and CRC between 1990 and 2024, with annotation of the population screening cohort (2014–2024). This study was approved by the Radboud University Medical Centre Research Ethics Committee (2022–16134).

CASE REVIEW

All cases were histologically reviewed, with special attention to the presence of a precursor lesion and signet ring cells. The presence of intraepithelial lymphocytes was scored. For all patients, clinical information was collected including age at diagnosis, sex, location of the lesion, the method of detection (within or outside the population screening program), the presence of comorbidity or risk factors (polyposis, Lynch syndrome, IBD, radiation) and the presence of additional colorectal lesions at diagnosis and during follow-up.

MISMATCH REPAIR EVALUATION

Slides were stained automatically (Dako Omnis, Agilent, Santa Clara, CA, USA) with antibodies against MLH1 (1: 40, clone G168-15; BD Biosciences, San Jose, CA, USA), MSH2 (1: 20, clone GB12; Calbiochem/Merck, Darmstadt, Germany), MSH6 (1:200, clone EPR3945; Abcam, Cambridge, UK), and PMS2 (1:20, clone A16-4; BD Biosciences). Cases were considered mismatch repair-proficient (pMMR) if nuclear staining of neoplastic cells was present. Cases with loss of staining in neoplastic cells of at least one MMR protein with positive internal control cells were considered mismatch repair deficient (dMMR).

RISK OF LYMPH NODE METASTASES BASED ON MISMATCH REPAIR STATUS

The risk of lymph node metastases for intramucosal carcinoma is hard to estimate because of the low incidence. In order to provide some guidance for decision making, we estimated the lymph node risk per T

Table 1. Clinicopathological characteristics of the included cases

	Patients				Histology				MMR status				Follow-up		
	Age	Sex	Risk factors	Location	Polyp type	Size	SRC	IEL	MLH1	PMS2	MSH2	MSH6	Colorectal pathology	Other cancers	Follow-up
A	55[a]	F	None	Sigmoid	TSA	1.3	Yes	No	No loss	No loss	No loss	No loss	None	None	Resection, N0
B	54	F	CHEK2 deficiency	Sigmoid	TSA	2.5	Yes	No	No loss	No loss	No loss	No loss	4 TA	4×	Surveillance, NED
C	70	M	IBD	Sigmoid	TA	2.0	Yes	No	NA	NA	NA	NA	10 TVA	None	Resection, N0
D	72	M	Polyposis	Sigmoid	TVA	2.5	Yes	No	No loss	No loss	No loss	No loss	3 CRC, 10+ TA	None	Died with metastatic CRC
E	70[a]	F	None	Sigmoid	TA	2.5	Yes	No	No loss	No loss	No loss	No loss	None	None	Surveillance, NED
F	52	M	Lynch	Coecum	TVA	2.5	Yes	No	Loss	Loss	No loss	No loss	6 TA, 1 CRC	None	Resection, N0
G	72[a]	F	None	Transverse	SSL	0.2	Yes	Yes	Loss	Loss	No loss	No loss	None	None	Surveillance, NED
H	57[a]	F	Lynch	Unknown	TA	0.9	No	Yes	No loss	No loss	Loss	Loss	8 TA	Endometrial ca	Surveillance, NED
I	55	M	Lynch	Ascending	TA	0.3	No	Yes	No loss	No loss	Loss	Loss	6 TA	Gastric ca	Died with NED
J	44	M	Lynch	Coecum	TA	1.4	No	Yes	No loss	No loss	Loss	Loss	2 TA	None	Resection, N0
K	64[a]	F	Polyposis	Sigmoid	TA	1.5	No	No	No loss	No loss	No loss	No loss	13 TA	None	Surveillance, NED
L	45	M	Lynch	Sigmoid	TA	0.2	No	Yes	No loss	No loss	Loss	Loss	4 TA	None	Surveillance, NED
M	63[a]	M	Polyposis	Rectum	TA	0.7	No	No	No loss	No loss	No loss	No loss	16 TA	None	Surveillance, NED
N	43	M	Lynch	Rectum	TA	0.5	No	Yes	Loss	Loss	No loss	No loss	None	None	Surveillance, NED

The patient with biallelic germline pathogenic variants in *CHEK2* presented with thyroid, kidney, breast, and endometrial cancer. Letters correspond to Figure 1.

CRC, colorectal carcinoma; F, female; IBD, inflammatory bowel disease; IEL, intraepithelial lymphocytes; M, male; MMR, mismatch repair; NA, not assessable; NED, no evidence of disease; SRC, signet ring cells; SSL, sessile serrated lesion; TA, tubular adenoma; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma.

[a]Detected in the population screening program.

category for dMMR and pMMR cases, within and outside the population screening program in the Netherlands. We used a retrospective cohort from the nationwide Dutch pathology database (Palga) registered under LZV2024-128. All patients diagnosed with a single CRC between 2014 and 2018, and aged 55–70 years old were eligible for inclusion. Descriptive statistics were used.

Results

Of the 134 cases identified by our search strategy, the vast majority did not present with intramucosal CRC, but showed either HGD (n = 97 [72.4%], with a relatively high number of traditional serrated adenomas, n = 19 [19.6%]) or invasive carcinoma at surgery (n = 23, 17.2%). We identified 14 cases (10.4%) of true intramucosal carcinoma, in which all three observers independently and unanimously agreed on, four cases were consultation cases from other hospitals (Table 1).

Our patients included six females and eight males, with an average age of 58.3 years (range 43–72 years). Most intramucosal carcinomas developed in conventional adenomas (two tubulovillous adenomas, nine tubular adenomas); two cases of traditional serrated adenomas, and one case in a sessile serrated lesion (Figure 1). Most cases were located in the right colon (9/14, 64.2%). The mean size of the polyp was 1.4 cm (range 0.2–2.5 cm). In 7/14 (50%) cases, signet ring cells or poorly cohesive foci were present (Figure 1).

In one patient MMR status could not be determined due to lack of material (small tumour focus). In seven patients (50%) mismatch repair deficiency was present, in 6/7 associated with Lynch syndrome (85.7%). Most of these patients showed intraepithelial lymphocytes. *MLH1* hypermethylation was confirmed in the sessile serrated lesion (SSL). Five additional patients were identified with an increased risk for CRC: one patient with IBD, one patient with biallelic germline pathogenic variants in *CHEK2*, and three patients with polyposis (defined as at least 10 adenomas before the age of 70).

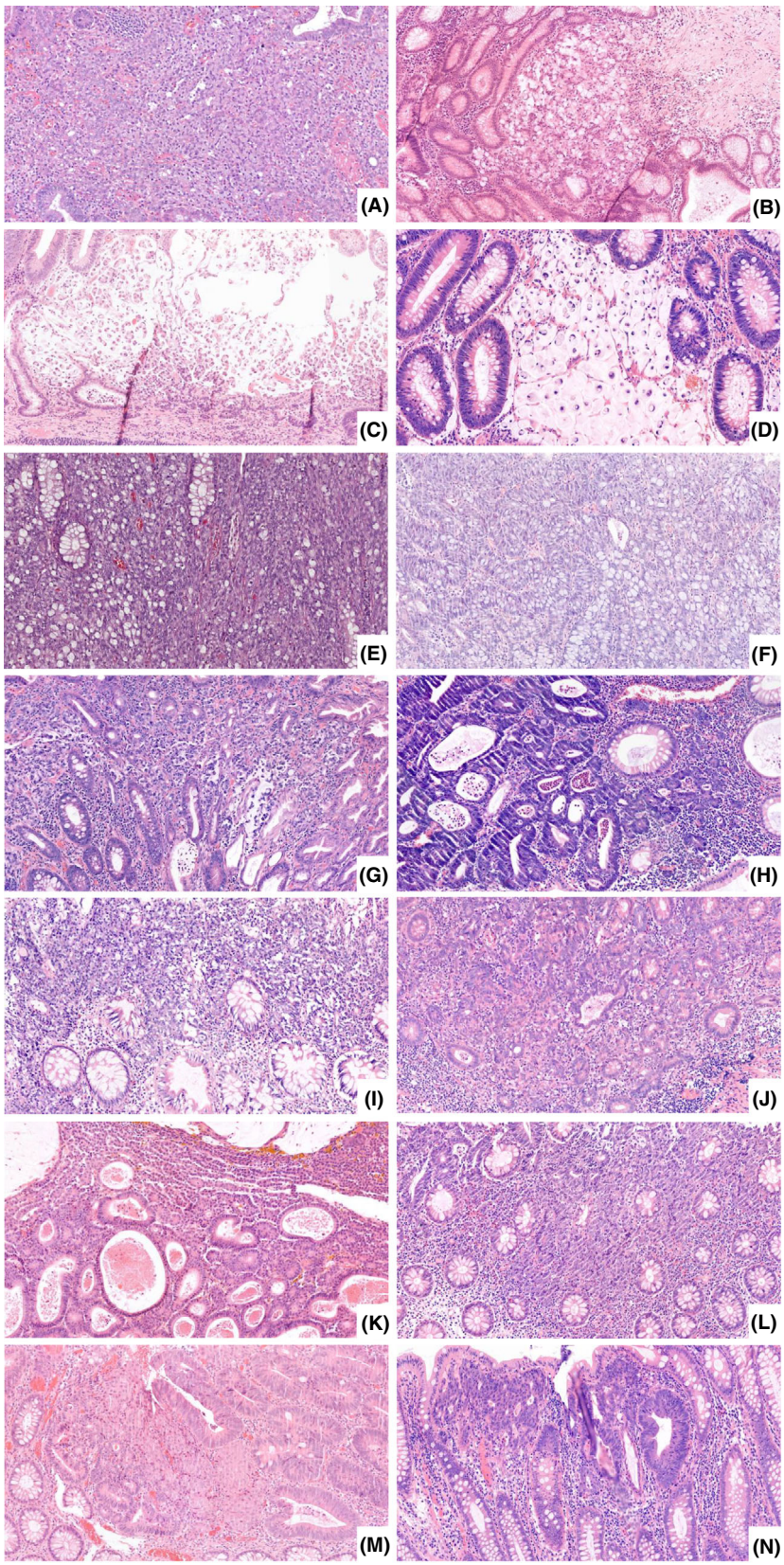
Between 1990 and 2024, 2133 patients with HGD in adenomas and 9502 individual patients with CRC were diagnosed at the Radboudumc, leading to a relative incidence of intramucosal carcinoma of respectively 0.7% in cases with HGD and 0.1% in cases with CRC. In our local population screening cohort, we received histological biopsies and excisions from 7031 patients, 420 were diagnosed with HGD, 516 with CRC. From our 14 patients, 6 were detected within the population screening, leading to a relative incidence of intramucosal carcinoma of respectively 1.4% of HGD and 1.1% of CRC. By extrapolation, 0.09% of cases in the population screening might be diagnosed as intramucosal carcinomas.

To determine the potential risk of lymph node metastases, we performed a national search for all histological diagnosed CRC with a resection and identified 13,689 patients with a known MMR status, 1511 patients with dMMR CRC (11.0%). dMMR was more frequent in females (14% vs. 6.6%, $P < 0.001$) and in proximal CRC (25% vs. 3.1% in distal CRC, $P < 0.001$). Within the population screening group, 499 patients with dMMR (10.5%) and 4244 patients with pMMR were identified. Risk of lymph node metastases per T category were lowest in the pT1 group and highest in the pT4 group, as expected. Percentages were lower in the population screening (34.8% N+ vs. 39.5% N+, $P < 0.001$) and the dMMR groups (Figure 2), with only 5.7% node positivity in the dMMR pT1 group and 15.9% in the pMMR pT1 group ($P < 0.001$). We did not include the pT1 cases with local excision due to the lack of information on the lymph node status, so the actual numbers with lymph node metastases might be lower than those reported here.

Discussion

In this study we have shown that intramucosal colorectal carcinoma presents in patients with an increased risk for CRC development, either in the context of IBD or a hereditary cancer syndrome. In line with these findings, there was a very high incidence of dMMR in intramucosal carcinoma (50%), almost five times the incidence observed in the general CRC population (11%). This warrants the acknowledgement of intramucosal carcinoma as a rare but

Figure 1. The 14 intramucosal carcinoma cases illustrating the variability in morphology. (**A**,**B**) intramucosal signet ring cell carcinoma, (**C**, **D**) signet ring cells in extracellular mucin, (**E**,**F**) goblet cell/signet ring cell proliferation in solid fields and glands, (**G**–**K**) small glands, poorly differentiated clusters, and tumour budding, (**L**–**N**) more solid growth pattern. Letters correspond with Table 1. In K, neuroendocrine stains were negative. H&E stain.



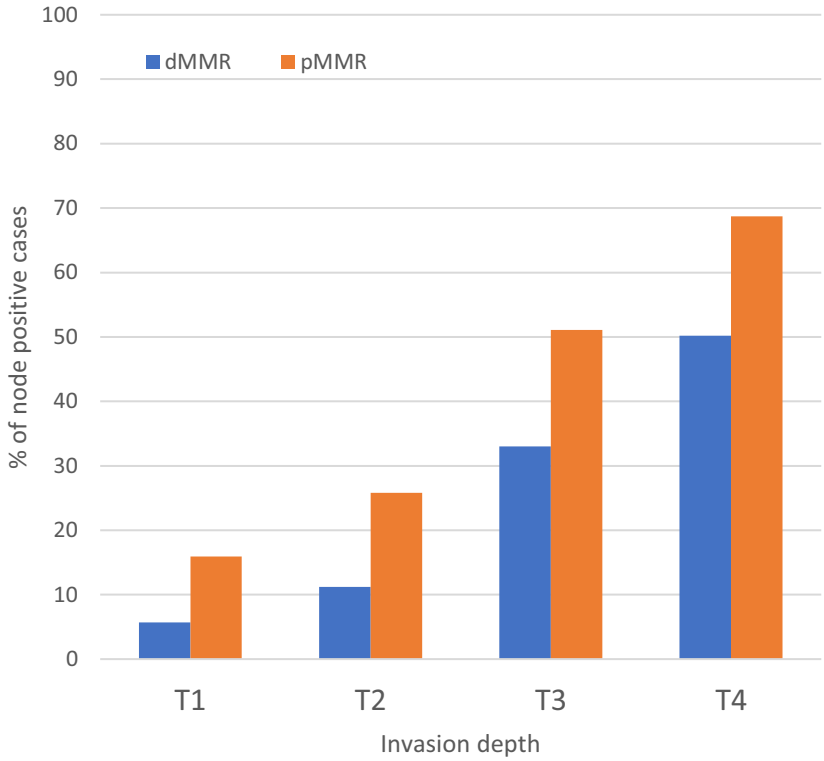


Figure 2. Relation of invasion depth and mismatch repair status with the risk of lymph node metastases in all Dutch patients diagnosed with colorectal carcinoma between 2014 and 2018.

relevant diagnosis. In line with this finding, MMR staining is recommended in those cases diagnosed as intramucosal carcinoma.

It is essential to distinguish intramucosal carcinoma from high-grade dysplasia. We observed a relatively high number of incorrectly diagnosed intramucosal carcinomas in traditional serrated adenomas. This is easily understood, given our long inclusion period. Although traditional serrated adenomas were already described in 1990,[20] their routine diagnosis has been suboptimal over the years[21] and it is likely that the presence of ectopic crypts leading to a more complex architecture, including cribriform structures, were considered carcinoma *in situ* in the past. It is also essential to diagnose intramucosal carcinoma only in excisions where the whole lesion can be appreciated. Diagnosis of intramucosal carcinoma in biopsies might lead to underestimation of the true nature of the underlying malignancy, as was the case in 17% of our series and also has been described before.[10] It would make more sense to categorize these as suspicious for malignancy.[22]

The high incidence of dMMR in intramucosal carcinoma is remarkable, compared to the very low incidence in advanced adenomas. We have previously shown that, although a significant part of conventional adenomas in Lynch syndrome patients show dMMR,[23] the percentage of dMMR in an unselected cohort of screen-detected advanced adenomas is very low (0.3%).[24] The strong association with dMMR and Lynch syndrome in our cohort and others[17,19] illustrates thus not only the need to diagnose intramucosal carcinoma, but also the indication for MMR analysis in this patient group.

It is good to realize that intramucosal colorectal carcinoma is a very rare diagnosis. One of the main limitations of this study is the lack of a true estimation of incidence. Based on our estimations, the incidence might be less than 1 in 152 adenomas with high-grade dysplasia or less than 1 in 680 CRC. These might be even overestimations, since our laboratory is a tertiary referral centre for both hereditary cancer and population screening. Acknowledgement of the differences between Eastern and Western diagnosis of colorectal carcinomas[2,3] might explain global differences in incidence. In line with our findings, a large cohort of Lynch syndrome patients showed a high incidence of intramucosal carcinomas (10.4%)[19] amongst all colorectal

lesions. A Japanese cohort of IBD patients showed four patients with an intramucosal poorly differentiated or signet ring cell component (3.8%).[18] The increased incidence in these high-risk populations is expected. The variation in the general population is less easy to explain. In the registry-based study[9] the incidence of *in situ* carcinoma was 5.4% of all CRC or 2.2% if only those with a known N0 status were included. The recent French series[11] based on the national population screening program described a 26.6% intramucosal carcinoma rate. However, only 55 intramucosal carcinomas (5% of their cases) underwent a resection and no pathologists seemed to be involved in this study. The relative lack of a larger series in the literature and evidence from daily practice suggest that this is an overestimation.

To avoid both over- and underdiagnosis of intramucosal carcinoma, it is essential to standardize this diagnosis. In line with other gastrointestinal diagnoses, the minimal requirement is *unequivocal infiltrative growth in the lamina propria, which might be most easily recognized in cases with overt poor differentiation or formation of signet ring cells or tumour budding*, which is also in line with the existing literature on this topic.[2,15,16,18] Cases with invasion in the muscularis mucosae but not beyond can also fall into this category. Special attention should be given to signs pointing towards deeper invasion, including locoregional spread. It has been suggested that intramucosal carcinoma can present with submucosal lymphovascular invasion,[8] intramural vascular invasion,[25] or even lymph node metastases.[26] Given the presence of tumour beyond the lamina propria, it seems reasonable to consider these cases as invasive carcinoma, with the associated risks of metastases and recurrence, rather than underdiagnosing them as intramucosal carcinoma.

As is evident from our series, as well as the literature,[11,12,15] the risk of lymph node metastases and recurrence is very low in intramucosal carcinoma. This is in line with population findings that show a decreasing risk of lymph node metastases in relation to decreasing invasion depth (Figure 2); this risk is particularly low in cases with dMMR. This suggests that additional surgery, although frequently applied in these cases, is not indicated for the treatment of the intramucosal carcinoma itself. However, in Lynch syndrome patients extensive surgery can also be applied to prevent metachronous cancer.[27] A word of caution should be reserved for the presence of intramucosal carcinoma in fragmented polyps, since more extensive invasion is hard to rule out in these cases.

In conclusion, we have shown that the main reason to diagnose intramucosal carcinoma is the identification of high-risk patients. This diagnosis is very rare, and the outcome of the patients is good.

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MEVB, RSvdP, and IDN designed the study and performed the analyses. All authors provided the acquisition of the cases. All authors provided interpretation of data, writing, review, and revision of the article. All authors read and approved the final article.

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Conflict of interest statement

None declared.

Data availability statement

The data from this study are available from the authors upon reasonable request.

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