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OPINION REVIEW

Computed tomography colonography and radiation risk: How low can we go?

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Abstract

Computed tomography colonography (CTC) has become a key examination in detecting colonic polyps and colorectal carcinoma (CRC). It is particularly useful after incomplete optical colonoscopy (OC) for patients with sedation risks and patients anxious about the risks or potential discomfort associated with OC. CTC's main advantages compared with OC are its non-invasive nature, better patient compliance, and the ability to assess the extracolonic disease. Despite these advantages, ionizing radiation remains the most significant burden of CTC. This opinion review comprehensively addresses the radiation risk of CTC, incorporating imaging technology refinements such as automatic tube current modulation, filtered back projections, lowering the tube voltage, and iterative reconstructions as tools for optimizing low and ultra-low dose protocols of CTC. Future perspectives arise from integrating artificial intelligence in computed tomography machines for the screening of CRC.

Key Words: Computed tomography colonography; Colorectal cancer; Radiation risk; Image quality; Image noise; Iterative reconstruction

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Core Tip: Computed tomography colonography (CTC) is an important imaging technique with significant advantages over optical colonoscopy in terms of less invasiveness, better compliance, and assessment of extracolonic structures. Ionizing radiation is the most significant burden of this technique. This opinion review comprehensively addresses the radiation risk in CTC with imaging technology refinements that should be used to lower radiation doses.

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INTRODUCTION

Computed tomography colonography (CTC), also referred to as a virtual colonoscopy (VC), was introduced in 1994 by Vining *et al*[1]. They were the first to describe this modified computed tomography (CT) examination of the large intestine as a diagnostic test for colorectal carcinoma (CRC) and polyps[2]. Since then, CTC has become an examination of crucial importance in imaging polyps and potential CRC in patients not amenable to optical colonoscopy (OC). CTC has advantages over OC because of its less invasive nature, better patient compliance, and the ability to detect extracolonic disease[3]. Hence, CTC is an accepted screening test for CRC and is growing in its utilization. We have to be aware that no CTC findings allow us to distinguish adenomas from non-neoplastic polypoid lesions such as hyperplastic or inflammatory polyps, making the histological study necessary in all instances. One of the drawbacks of CTC is usually missed flat lesions such as a flat polyp. Images that can be misinterpreted and can mimic polyps include untagged stool, partially distended haustra, or focally thickened folds[4].

On the other hand, OC is often associated with anxiety, fear, and discomfort compared to CTC, and carries a risk of being incomplete, especially in elderly patients[5]. Despite these advantages of CTC, ionizing radiation is the most significant burden of this technique (Table 1). However, imaging technology refinements, favorable cost analyses, and the impact of extracolonic findings make this method a suitable alternative to OC for CRC screening[3].

CTC FOLLOWING INCOMPLETE OPTICAL COLONOSCOPY

One of the unanimously accepted CTC indications is to complete a colonic workup after an incomplete OC. Some 10% of colonoscopies cannot be completed for different causes: Neoplastic stenosis, diverticulosis, adhesions, loops, or redundant colon[6-9]. A study revealed that 4.3% of neoplasms were missed by incomplete colonoscopy and were found in additional imaging studies[6]. Moreover, the proximal colon study is particularly important in neoplastic stenosis, as the percentage of synchronous cancer is high (4%-5%)[10]. In some patients, OC can be technically challenging, with the inability to achieve cecal intubation, resulting in inadequate visualization of the entire colon, hence a potential risk of undetected colon cancer and polyps[11,12] Except radiology practices with an active screening program, incomplete OC examinations likely account for the vast majority of CTC requests[13]. Factors previously shown to contribute to the risk of incomplete OC include; increasing patient age, low body mass index, female gender, history of prior abdominal and pelvic surgeries, presence of severe diverticular disease, poor bowel preparation, the experience of the endoscopist, tumorous obstruction of the entire lumen and anesthesia-related complications[7].

There are two primary strategies regarding the timing of CTC following incomplete OC. The first and most common is same-day CTC utilizing the prior OC prep, often supplemented with oral contrast after recovery from OC[14]. This is often the more convenient option for the patient as they do not have to undergo further bowel preparation (assuming bowel prep for OC was adequate) and return on a separate day. CTC is usually performed 2–3 h later. Another option is to have the patient return for CTC at a later date utilizing a standard CTC bowel regimen with an osmotic

Table 1 Advantages and limitations of computed tomography colonography

Advantage	Limitation
Minimally invasive procedure	Exclusively diagnostic method
Safe procedure	Ionizing radiation
No need for sedation	Fecal residue simulate pathology
Short examination time	Laxative residue simulate pathology
Assess to extracolonic disease	Flat lesions
Three dimensional view	
View of the entire colonic surface	
Access to post-obstructed bowel	
"Second look"	

cathartic and dual agent tagging protocol. CTC should be delayed if an endoscopic resection has been performed during OC[15].

SCREENING FOR CRC

Most population-based screening programs for CRC target the age range from 50 to 74 years old and include indirect screening, such as fecal occult blood testing or direct visualization with flexible sigmoidoscopy or OC[16]. The most common is the stool test-based screening [guaiac fecal occult blood test (FOBt) or fecal immunochemical test (FIT)] due to its low cost, availability, safety, and easy transport (*via* post). If positive, FOBt and FIT are usually followed by OC to confirm neoplasia or suspect polyps[5].

Since CTC has become an available alternative option to OC, more patients choose CTC as a more desirable option. In a multicenter survey of 1417 individuals, 68% chose CTC over OC due to its less invasive nature, and 47% chose CTC to avoid the risks associated with OC[17]. Another Dutch study showed that 93% of patients would choose another CTC after the initial one[18].

The CRC screening potential of CTC has been investigated in three European randomized trials: COCOS study in the Netherlands (CTC *vs* OC)[19], SAVE[20], and PROTEUS[21] studies in Italy.

The SAVE study compared reduced preparation and full-preparation CTC, FIT, and OC, while the PROTEUS study compared CTC *vs* sigmoidoscopy. The participation rates, positivity rate, and CTC detection rates were similar amongst the studies. The participation rate for screening CTC was higher than that for an OC, with a slightly lower detection rate, but with comparable yield per invitee. The participation rate for screening CTC was much lower than that for FIT, but its detection rate was three-fold that of one FIT round. CTC and sigmoidoscopy showed similar participation and detection rate. These results encourage CTC implementation in screening programs for CRC[22].

RADIATION INDUCED RISKS

CTC's main disadvantage is ionizing radiation, especially since CTC has been considered a CRC screening tool. Radiation dose significantly determines CT image quality, its diagnostic accuracy, and clinical utility. Strategies for lowering radiation dose are utilized to maintain and improve image quality. The dose should only be reduced if one can preserve the diagnostic image quality for the specific pathology. It is essential to understand the relation between image quality and radiation dose to optimize the radiation dose in CTC[23].

CTC dose is lower than the conventional CT examination, about one half of the dose, because of high natural contrast between the soft tissue of the colonic wall, luminal gas, and tagged fecal residue and fluids[6].

To give the proper insight, it is meaningful to compare the doses of different diagnostic procedures with the chest X-ray dose or years of exposure to natural background radiation, ranging from 1 to 3 mSv/year, depending on the geographical

region. Thus, mammography has a dose of 0.13 mSv, which corresponds to 6 chest X-rays or 14 days of background radiation. An average abdominal CT has 5-25 mSv, which corresponds to 250-1250 chest X–rays or 2-11.5 years of background radiation, depending on the number of phases that have to be scanned to confirm the suspect diagnosis[24] (Table 2).

During the last few decades, physicists, radiologists, and technologists have studied CT technology to find ways to reduce radiation doses for specific "diagnosis-related" CT examinations. Currently, we have well-established "diagnosis-related" protocols such as "low-dose" kidney stone dedicated protocol, "low-dose" lung cancer screening protocol, *etc*.

Dose reduction can be achieved in two ways. Firstly it is crucial to appropriately target image quality for a specific diagnostic test, not demanding lower noise or higher spatial resolution than necessary. For instance, in a high-contrast setting, as in the detection of colon polyps from a background of air and contrast-tagged stool[25,26], it allows high noise level and relatively low radiation dose without sacrificing the diagnostic confidence. Detection and characterization of low-contrast lesions present in CT imaging of hepatobiliary and brain pathology require a relatively low noise level and higher radiation dose. Consensus agreement on image quality requirements exists in guidelines and standards[27], but precise quantitative requirements exist only for several examinations[28].

There are many ways to adjust scanning parameters in order to lower the dose. One way to reduce the dose is to change the technical exposure parameters of scanning: The tube current or the voltage depending on the tissue density and contrast, scanning region, and the patients' body shape and size[29].

Modern CT equipment can automatically modulate the X-ray tube current after obtaining a scanned region's initial topogram, known as automatic tube current modulation (ATCM). ATCM adjusts the X-ray tube current (mAs) according to the size and the attenuation of the examined body part. It has been recommended to use ATCM for CTC[5,20,21].

Each time the scanning parameters are changed, it influences the image's quality, namely spatial and/or contrast resolution, which are important for detecting specific pathologies. Spatial resolution relates to sharp boundaries of the tissues, organs, or structures, while contrast resolution involves the difference in contrast of various tissues (*e.g.*, normal or pathologically altered). Low dose protocols have a higher image noise due to altered (lower) electrical conditions. Spatial or contrast resolution is sacrificed, and the radiologist has to get the same information from granulated images. Therefore, it is important to balance the dose by adjusting electrical conditions and maintaining image quality. The image quality needs to be good enough to distinguish pathologic lesions from normal structures. Thus, it is crucial to find a delicate balance between the lowest dose and acceptable image quality, making it possible for a radiologist to discern pathologic structures[5]. This is also referred to as the As Low As Reasonably Achievable principle, well established in the area of radiation protection[23]. In addition to altering exposure parameters, software options have been developed to make less image noise by keeping the tube current as low as possible. These software reconstructions techniques are Sinogram-Affirmed Iterative Reconstruction (SAFIRE) and a conventional filtered back projection. These techniques allowed the use of even lower doses of radiation than the conventional low dose (LD) protocol named ultra-low dose (ULD) with maintained image quality[5,24,30]. In 2018, a study evaluating the ULD protocol's diagnostic value in detecting polyps[31] showed that the ULD protocol lowers the effective dose up to 63.2% compared to LD protocol (0.98 mSv for ULD and 2.69 mSv for LD). Image noise measurements with ULD were slightly lower (28.6) than with LD (29.8) (P = 0.09). Image quality was not different between 2D and 3D with either ULD and LD. A special 3D software option must be used to navigate the large bowel and when interpreting CTC to help detect intraluminal lesions. In contrast, the 2D option is the routine CT examination technique. Polyp detection was also comparable, with no significant difference in detection rate and polyp measurement for LD and ULD protocols[30]. Therefore if iterative reconstruction methods (the software option in almost all modern CT scanners) were included during the scanning, there was no significant image quality degradation with ULD-CTC compared with LD-CTC.

Advantages of specific computer software for CTC interpretation, which enables dynamic viewing of two-dimensional axial images, multi-planar reformats, and three-dimensional renderings, require radiologists' interactive training. The radiologist can use either 2D axial images or 3D renderings for CTC's primary interpretation, with the alternate method reserved for problem-solving specific questions related to a potential lesion. 3D reading is an additional software option that enhances polyp detection and

Table 2 Comparison of different ionizing radiation doses for different examinations

Examination	Ionizing radiation dose [mSv]
X-ray lung	0, 1
X-ray abdomen	1
Barium enema fluoroscopy exam	9
CT abdomen and pelvis (w/o contrast)	10
CTC (2 series)	20
CTC ultra low-dose protocol	2

CT: Computed tomography; CTC: Computed tomography colonography.

decreases the interpretation time without increasing the patient dose (Figure 1).

Skilled usage of these techniques acquired by comprehensive training correlate with polyp detection sensitivity[31]. Primary 2D interpretation is rendered from magnified colonic axial images gained in supine and prone positions. Compared to primary 3D interpretation, it shortens the assessment time of lesion density and homogeneity.

Sessile polyps have round or ovoid morphology and are of soft tissue density. They remain fixed in location on the colon wall in both the supine and prone images. The stool can be differentiated from polyps since it is typically mixed density and shifts location when the patient changes position. Pedunculated polyps can shift in location when the patient moves from supine to prone positions, but the stalk is typically easily identified on 2D and 3D images. Multiplanar reformats and 3D images are useful for evaluating lesion morphology and confirming polyps[32].

In addition to widely used techniques of lowering radiation dose such as automatic tube dose modulation (automatic adjustment after the initial topogram), lowering the tube current, and applying iterative reconstruction (IR), lowering tube voltage can be useful. This option is rarely used for routine CT scanning because it impairs X-ray penetration through the scanned region. However, during the CTC, the bowel has a high contrast due to intraluminal gas; therefore, high voltage is not needed. If there is an option for IR, we can lower the voltage and turn on IR. The iterative reconstruction software option will fix the image noise which arises from the lower voltage[29].

The data suggest that low tube voltage with IR results in a 27 % radiation reduction while maintaining the image quality and detection (100kVp *vs* 80kVp)[33]. In addition, new IR such as SAFIRE could lower the voltage even more[30].

Recent studies show that both hybrid and iterative model reconstruction techniques are suitable for sub-milliSievert ultralow-dose CTC without sacrificing the study's diagnostic performance[34].

Several operational factors typically result in higher doses. Repeated CT scanning, such as multiphase examinations, increases the radiation dose. For example, suppose diagnostic CTC is being performed in a patient with suspected colorectal carcinoma. In that case, intravenous contrast may be necessary, and CT acquisition parameters will typically require higher mAs. If the patient is undergoing CTC as a screening examination, then intravenous contrast is not routinely used.

Patient's hight and/or length also influences the radiation dose. Longer scan length results in radiation exposure to a greater anatomic region and hence higher radiation dose. For some reason, for a detailed analysis, radiologist could request thinner images that provide better image resolution and improved visibility of small objects. However, beam intensity needs to be increased to reduce the noise in these thinner images, which concurrently increases the radiation dose[35].

Since the whole abdomen is visible during CTC screening, many abnormalities outside of the colon can be picked up. Several US screening studies collected the data on clinically significant extracolonic findings that required further imaging. The proportion of patients with follow-up CT scans to investigate these findings was in the range of 5-10%[36,37]. The most common follow-up scan were; an abdomen CT scan and abdomen/pelvis and chest CT scans. The dose from an abdomen/pelvis CT scan performed with and without contrast is about 20 mSv[38], which will result in a radiation risk that is about twice as high as the risk from CTC. However, as only a small proportion (*e.g.*, 10%) of the screening population will receive these additional scans, it is unlikely that they will increase the average risk to the whole screening population by more than 20%.

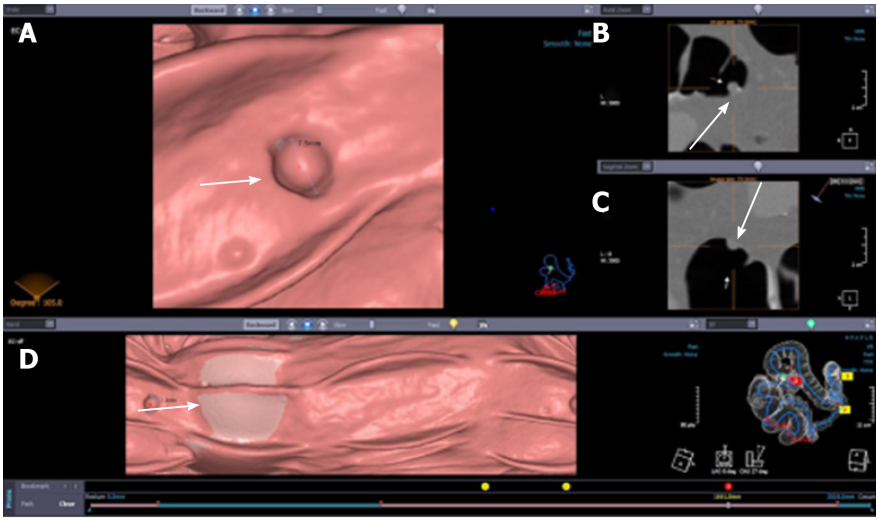

Figure 1 Computed tomography colonography: Two- and three-dimensional view of the polyp (arrows). A: Polyp 3D view; B: Polyp 2D view; C: Polyp 2D view; D: Tagged stool.

The standard American College of Radiology (ACR) CTC protocol[39-42] specifies that the patient be scanned in both the supine and prone positions to allow complete evaluation of the colon with the dependent shifting of luminal fluid and complementary distention of non-dependent colonic segments. In a minority of cases, the same colonic segments will be collapsed on the standard positions, necessitating a third series to achieve full diagnostic evaluation. The sigmoid and/or descending colon account for most non-diagnostic segments, necessitating a right lateral decubitus series to complete the examination[43,44].

The frequency for performing a decubitus series at CTC varies considerably according to study indication, practice site, patient age, BMI, and over time. It is critical to note that the CT technologist is primarily responsible for determining the need for a decubitus series–not the radiologist. These results have important implications for clinical practice, including the need for improved training and feedback for CT technologists[45].

Furthermore, practice regarding ancillary imaging before a CTC and after incomplete OC should be discussed as this can also increase radiation dose; for example, some centers perform a scout/topogram or non-contrast CT abdomen following incomplete OC, in order to exclude a perforation; although there is evidence to suggest this is unnecessary.

Perforation is a recognized complication of colonoscopy. Reported perforation rates range from one case in 3115 procedures (0.032%) to one case in 510 procedures (0.196%)[46-49]. The short time between incomplete colonoscopy and same-day or next-day CTC may not be adequate to allow some perforations to become clinically apparent. Because of the risk of exacerbating a clinically unsuspected perforation during insufflation at CTC, which can increase sepsis risk, screening for the presence of extraluminal gas before insufflation for CTC may benefit occult perforation among these patients. Colonic perforation after colonoscopy can be clinically occult. Recent studies have shown that some findings justify performing low-dose diagnostic CT before rectal tube insertion and gas insufflation in all patients referred for same-day or next-day CTC after incomplete colonoscopy to minimize the risks associated with exacerbating perforation[50].

RADIATION DOSE AND CANCER RISK

Effects of radiation and its risk are usually estimations based on the linear extrapolation of the cancer risks associated with ultra-high doses from Hiroshima and Nagasaki atomic bomb survivor studies[51]. Still, there is no unambiguous evidence of cancer induction at low dose levels, and the issue remains highly controversial.

In 2016, the Health Physics society published that radiation lower than 100mSv did not impact the human body[52]. Assuming that the CTC dose is on average 5mSv, that means that the theoretical cancer risk would be 0.04% in 50-year-old patients and

0.02% in 70-year-old patients after initial screening[51]. Keeping in mind that a lifetime risk for developing colon cancer is around 5%, CTC's benefits outweigh its estimated radiation risk. CTC doses are, currently, in many institutions, even lower than 3mSv, the dose which is comparable to annual radiation exposure in some countries such as the United States[53].

Since the age for screening for CRC is above the age of 50, exposure is decreased significantly, and therefore the radiation-related cancer risk is even lower. Since the proportion of dividing human cells decreases with age, this further raises CTC's safety in the older population it mainly serves[54].

It is important to consider the average frequency of each examination in the population and the average radiation dose with each technique to understand the radiation dose of CTC in the context of other ionizing techniques. However, all examination-based techniques (radiography, fluoroscopy, CT, positron emission tomography-CT, scintigraphy, and interventional cardiology) constitute 34 % of the total annual population dose[53,55].

It is important to emphasize that CTC is quite different from the usual CT examination. Inherently high contrast between the air-filled lumen of the colon and the soft-tissue attenuation of the colonic wall allows a relevant dose reduction without loss of diagnostic accuracy[54].

CONCLUSION

In addition to CTC's high safety profile, slightly better patient compliance, ability to detect extracolonic disease and comparable polyp and cancer detection rate to OC, CTC can be performed with a minimal radiation dose that poses no risk of cancer to the patient.

CTC "good practice" should include individualizing the scanning technique according to the patient's attenuation level and using suitable tube potential selected by advanced automatic exposure control techniques that adjust the tube current. Implementation of iterative reconstruction in everyday clinical practice can bring significant image quality improvement and radiation dose reduction over conventional filtered back-projection-based reconstruction algorithms.

Modern CT equipment allows us to scan CTC at much lower doses ranging from 1 to 5 mSv. These doses are comparable with 1-2 Lung radiograms and are on the annual radiation background level in some countries. Since screening programs mostly include two readers (two experienced radiologists) and "double-blinded" reading, the new perspectives arise from the integration of artificial intelligence in CT machines, which could be used for screening CTC instead of a "second reader".

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SYSTEMATIC REVIEWS

Post-colonoscopy diverticulitis: A systematic review

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Abstract

BACKGROUND

Post-colonoscopy diverticulitis is increasingly recognized as a potential complication. However, the evidence is sparse in the literature.

AIM

To systematically review all available evidence to describe the incidence, clinical course with management and propose a definition.

METHODS

The databases PubMed, EMBASE and Cochrane databases were searched using with the keywords up to June 2020. Additional manual search was performed and cross-checked for additional references. Data collected included demographics, reason for colonoscopy, time to diagnosis, method of diagnosis (clinical *vs* imaging) and management outcomes.

RESULTS

A total of nine studies were included in the final systematic review with a total of 339 cases. The time to diagnosis post-colonoscopy ranged from 2 h to 30 d. Clinical presentation for these patients were non-specific including abdominal pain, nausea/vomiting, per rectal bleeding and chills/fever. Majority of the cases were diagnosed based on computed tomography scan. The management for these patients were similar to the usual patients presenting with diverticulitis where most resolve with non-operative intervention (*i.e.*, antibiotics and bowel rest).

CONCLUSION

The entity of post-colonoscopy diverticulitis remains contentious where there is a wide duration post-procedure included. Regardless of whether this is a true complication post-colonoscopy or a *de novo* event, early diagnosis is vital to guide

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appropriate treatment. Further prospective studies especially registries should include this as a complication to try to capture the true incidence.

Key Words: Colonoscopy; Diverticulitis; Complication; Management; Antibiotics; Surgery

Core Tip: The entity of post-colonoscopy diverticulitis is a rare complication. However, there is no consensus on its definition especially on the duration included post-procedure. It could well represent a de novo event or exacerbation of subacute condition. Regardless, it should be considered as a differential in patients presenting with abdominal pain post-colonoscopy and managed according to the usual treatment of patients presenting with diverticulitis.

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INTRODUCTION

Colonoscopy is usually performed for the purpose of screening, diagnostic or surveillance. It is a relatively safe procedure with complication rate between 0.1%-0.3%[1,2]. Most large studies report mainly on complications such as bleeding, perforation and post-polypectomy syndrome[1,2]. Other rarer complications such as splenic injury and pancreatitis have also been reported[2,3]. In recent years, the entity of post-colonoscopy diverticulitis has emerged as a potential complication. Its exact incidence is not known but estimated to be around 0.04%-0.08%[1]. The underlying pathogenesis is not known as a few theories have been hypothesized.

This entity is likely to be progressively more significant due to the exponential increase in number of colonoscopies performed worldwide from colorectal screening programmes and the improved life expectancy of the global population which coincides with higher incidence of diverticular disease[4]. This is evident in the study from Guertin *et al*[5] where there were 4066 more screening and surveillance colonoscopies in the last 2 years of the study period as compared with the first 2 years (13841 in 2015-2016 *vs* 9755 in 2013-2014, $P = 0.005$).

With no uniform and clear definition of this entity, the aim of this study was to systematically review all available evidence of post-colonoscopy diverticulitis and described its incidence, clinical course and to propose a definition.

MATERIALS AND METHODS

A systematic review of the literature from the January 1990 to June 2020 was performed by searching PubMed, EMBASE and Cochrane databases. The medical subject headings (MeSH) and keywords used individually or in combination were: "diverticulitis", "colonoscopy", "post-colonoscopy", "colonoscopy-induced", "perforation" and "complication". All references were searched and cross-checked. All foreign language articles if available were translated by medical personnel with proficiency in both foreign language and English. Ethics approval was not required from the institution's ethics committee for this study.

The search pathway is described as per the PRISMA flowchart as shown in Figure 1.

Inclusion and exclusion criteria

A data proforma was designed prior to the collection of data for uniformity. The investigators (Ng ZQ, Tan JH and Tan HCL) individually collected the data. Any difference in opinion was resolved through discussion with the other author (Theophilus M) but was not required. The data collected included author, journal, year, country, demographics, reason for colonoscopy, time to diagnosis, diagnosis

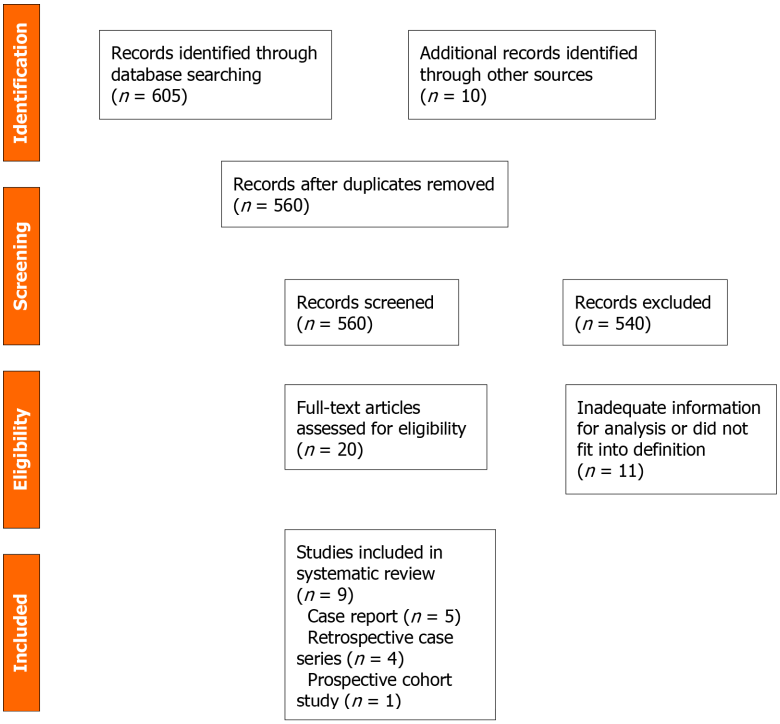

Figure 1 PRISMA flowchart of the search pathway for post-colonoscopy diverticulitis.

method (clinical or radiological), management (outpatient or inpatient, oral or intravenous antibiotics and radiological or surgical intervention) and recurrence of diverticulitis. Data were analyzed using descriptive statistics.

RESULTS

One prospective study[6], four retrospective cohort studies[7-10] and four case reports[11-14] were included in the final analysis, with a total of 339 cases reported in the literature.

The estimated incidence of post-colonoscopy diverticulitis from the four retrospective and one prospective study in this review was 1.3%.

Of the nine studies, only one was published before 2010[8]. Majority of the literature originated from the United States (n = 5)[6-8,10,11]. The rest were from Asia Pacific (n = 4)[9,12-14].

Definition and timeframe

None of the studies have a definition for the entity of post-colonoscopy diverticulitis. Two large studies considered the episode of diverticulitis induced by colonoscopy up to 30 d post-procedure. The other case reports considered it from 2 h to 16 d post-colonoscopy. Two studies did not specify the timeframe.

Demographics, clinical presentation and management (Table 1)

The larger studies did not report the mean or median age and gender distribution of the patients with post-colonoscopy diverticulitis. Only the individual cases reported them.

Only four case reports described the individual case presentations that were not completely typical of the usual presentations[11-14]. There was evidence of raised inflammatory markers (white cell count and c-reactive protein).

Six out of nine studies reported the method of diagnosis[6,7,11-14]. Of those reported, 60 patients were diagnosed with computed tomography (CT) scan and 12 based on clinical judgement. Another reported relied on self-reported symptoms and perceived diagnosis of diverticulitis[6]. The findings of CT scan were reported in six studies where 66 patients were classified as uncomplicated and 6 as complicated diverticulitis.

Six out of nine studies described the management of the patients[7,8,11-14]. Of the six studies, only one patient was managed with outpatient oral antibiotics. Two patients needed percutaneous drainage. Surgical management was required in eight patients on the index presentation, but the type of operation was not specified. In a study of 68

Table 1 All the cases of post-colonoscopy diverticulitis reported in the literature from January 1980 to June 2020

Ref.	Type of study	Number of patient (s)	Age	Gender	Type of colonoscopy	Incomplete (I) *vs* Complete (C)	Reason for colonoscopy	Other concurrent intervention	Diagnosis of Post-colonoscopy diverticulitis	Findings on CT	Duration to diagnosis after scope	Symptoms	Biochemistry	Management
Levin *et al*[8] /United States/2006	Retrospective	6/16318	-	-	C	-	Screening or surveillance	Biopsy (n = 5)	-	-	Within 30 d	-	-	Inpatient antibiotics (n = 4), surgery (n = 2)
Ko *et al*[1]/ United States/2010	Prospective	23/21375	-	-	C	-	Screening and surveillance	-	Self-reported	-	Within 30 d	-	-	-
Rutter *et al*[10]/ United States /2012	Retrospective	82/43456	-	-	C	-	Screening and surveillance	Polypectomy (n = 41)	-	-	-	-	-	-
Park *et al*[13] /Korea/2013	Case report	1	44	M	C	C	Surveillance	Polypectomy and EMR	CT scan	Uncomplicated diverticulitis	2 h	Abdominal pain and fever	Normal WCC	Inpatient intravenous antibiotics
Lin *et al*[9] /Taiwan/2017	Retrospective	156/112543	-	-	C and F	-	Diagnostics and interventional	Biopsy (n = 6)	-	-	-	-	-	-
Park *et al*[14] /Korea/2016	Case report	1	65	M	C	C	Surveillance	Polypectomy	CT scan	Uncomplicated diverticulitis	48 h	Epigastric and left upper quadrant pain	Elevated WCC and CRP	Inpatient intravenous antibiotics
Gorgun *et al*[7]/ United States/2018	Retrospective	68/236377	56 (mean)	M:F = 25:43	C	I:C = 13:55	-	Polypectomy (n = 26)	CT scan	Uncomplicated (n = 62); Complicated diverticulitis (n = 6)	12 ± 8 d	Abdominal pain (n = 26), nausea/vomiting (n = 12), fever (n = 5), diarrhea (n = 5), chills (n = 3), PR bleeding (n = 2)	Elevated WCC	Antibiotics (n = 60), emergency surgery (n = 6), percutaneous drainage (n = 2)
Hudson *et al*[12] /Australia/2019	Case report	1	50	M	C	C	Diagnostics	Polypectomy	CT scan	Uncomplicated diverticulitis	16 d	PR bleeding, generalized abdominal pain	Elevated CRP	Inpatient intravenous antibiotics
Mohan *et al*[11]/ United States/2019	Case report	1	59	F	C	C	Screening	Polypectomy	CT scan	Uncomplicated diverticulitis	48 h	Left lower quadrant abdominal pain	Elevated WCC	Outpatient oral antibiotics

M: Male; F (gender): Female; CT: Computed tomography; C: Colonoscopy; F: Flexible sigmoidoscopy; WCC: White cell count; CRP: C-reactive protein.

cases, six cases subsequently had surgery after non-operative management[7].

Recurrence

Only one study[7] reported the follow-up of patients in recurrence of diverticulitis (26%).

DISCUSSION

Colonoscopy is a common procedure undertaken and has a relatively safe profile[15]. The common complications post-colonoscopy include bleeding, perforation and post-polypectomy syndrome[2,6,8,16]. Rarer complications reported include splenic injury, pancreatitis, mesenteric ischemia, cholecystitis and small bowel perforation[3]. This systematic review found that the entity of post-colonoscopy diverticulitis is a relatively rare complication with incidence slightly higher than previously estimated 0.11%-0.37%[6-10]. Nonetheless, the true incidence may be clouded due to under-recognition or misdiagnosis, and spontaneous resolution without invasive intervention. This is evident in large studies that this entity was not included in the main study objective[15].

The entity of post-colonoscopy appendicitis is likely to share some similarities in its pathogenesis[17]. Various theories have been postulated for its mechanism: Barotrauma secondary to insufflation, inadvertent intubation of the diverticulum, faecolith introduction or propagation during the procedure leading to inflammation and exacerbation of subclinical/chronic disease. In patients with history of diverticulitis, navigating the colonoscopy through the diseased segment of colon can be challenging and potentially lead to inadvertent intubation of the diverticulum[3]. The choice of gas insufflation (air *vs* carbon dioxide) is not known to be a risk. The pre-procedure mechanical bowel preparation has a potential role in altering the gut microbiome resulting in subtle defects in the mucosal barrier and subsequently leading to an inflammatory cascade following colonoscopy[4].

This entity is envisaged to be increasingly recognised due to the following reasons. The number of screening colonoscopies is expected to increase due to the colorectal screening programme for prevention of colorectal cancer where the screening population age coincides with the increased incidence of diverticular disease (> 50% of Americans older than 60 years of age have diverticular disease[4]). Besides, although the current evidence for follow-up colonoscopy after index episode of diverticulitis is contentious but most centres still do it as a routine 6-8 wk post-diverticulitis to ensure no underlying malignancy has been missed[18,19]. Taking into consideration the lifetime risk of diverticulitis in a person is approximately 10%-25%[20], a substantial number of the population will likely undergo a colonoscopic follow-up.

The clinical presentation of post-colonoscopy diverticulitis reported from the review was considerably variable with symptoms such as generalized abdominal bleeding, per rectal bleeding, nausea/vomiting and chills. The symptoms may be interpreted as non-specific and could overlap with other entities such as post-polypectomy syndrome. However, the main concern remains iatrogenic perforation especially in patients who had interventional procedures such as polypectomy, endoscopic mucosal resection or endoscopic submucosal dissection concurrently. The initial management should include a rapid assessment with resuscitation as required. Biochemistry examination maybe unremarkable initially but leucocytosis and a raised C-reactive protein maybe observed. The mainstay of imaging is CT scan of the abdomen/pelvis to exclude colonoscopic perforation or intra-abdominal organ injuries. It will help to confirm the diagnosis and guide further management.

The principles of management are no different to the usual presentation of diverticulitis[4,19]. In patients with uncomplicated diverticulitis, a short inpatient stay with intravenous antibiotics and bowel rest are usually sufficient. Depending on regional practice, in those that are clinically well, they could potentially be managed as outpatient with or without oral antibiotics[19,21]. The use of antibiotics can even be considered omitted in uncomplicated diverticulitis with no increased risk of complications[19,22]. In patients with localized complicated diverticulitis, non-operative management should be trialed upfront[19,23,24]. If there is evidence of large abscess > 4 cm, percutaneous drainage can be organised if accessible. In the clinically unstable patient, urgent surgical intervention should be undertaken.

This systematic review has been limited by the relatively small number of patients reported to have post-colonoscopy diverticulitis with variable duration reported after the colonoscopy. The entity remains unclear as: (1) It could represent an episode of *de novo* acute diverticulitis rather than a sequelae in those that reported up to 30 days

post-colonoscopy[6,8,12]; (2) It could also be an exacerbation of subclinical diverticulitis especially in those that underwent a colonoscopy 6-8 wk after an attack[4] and the information of history of diverticulosis or diverticulitis was lacking in the studies; (3) The symptoms can be easily overlooked and misdiagnosed if based on clinical grounds without confirmatory CT findings where some symptoms are commonly reported such as abdominal pain (10.5%), bloating (25%), diarrhea (6.3%), nausea (4%)[1] and lastly; and (4) A few studies correlated this entity based on ICD coding of diverticulitis from the database which may not be accurate[9]. This was also evident on a blog discussion post on New England Journal of Medicine Journal Watch in 2011[25].

Based on this systematic review, we propose the definition of post-colonoscopy diverticulitis as the occurrence of diverticulitis confirmed on CT scan within 72 h post-colonoscopy without the colonoscopic findings of acute or chronic diverticulitis and other pathology. The timeframe was chosen based on the definition of post-colonoscopy appendicitis which is believed to share some of the similar mechanism of pathogenesis.

A few key points raised from this systematic review: (1) It should be included in future audit of complications from colonoscopy; (2) The patients should be explained of this potential complication during the consenting process; (3) Patients with known history of diverticular disease, a difficult colonoscopy should be anticipated, and other methods should be tried to navigate the colonoscope through the diseased segment to prevent accidental intubation of the diverticula; and (4) The patients that had incomplete colonoscopy due to the abovementioned reason should be warned of the possibility of this complication on discharge.

CONCLUSION

The entity of post-colonoscopy diverticulitis is a relatively rare complication. The clinical presentation can mimic other common symptoms encountered post-colonoscopy. CT scan remains the imaging of choice to diagnose and guide further management. Majority of cases resolve with non-operative management. Endoscopists should be aware of this entity given the increasing number of colonoscopies performed.

ARTICLE HIGHLIGHTS

Research background

The number of colonoscopy performed worldwide is increasing steadily over the past decade for screening, diagnostics and surveillance purposes. Similarly, the incidence of diverticular disease is also increasing in the population.

Research motivation

The entity of post-colonoscopy diverticulitis as a complication of colonoscopy has been reported in the literature without clear description of definition, description, clinical presentation and management strategies.

Research objectives

The aim of this study was to systematically review all available evidence in the literature to propose a definition of post-colonoscopy diverticulitis, describe its incidence, clinical presentation, risk factors and management strategies.

Research methods

The systematic review was performed by searching the PubMed, EMBASE and Cochrane databases up to June 2020 and the references were manually cross-checked for additional references.

Research results

A total of nine studies were included in the final systematic review with a total of 339 cases. The time to diagnosis post-colonoscopy ranged from 2 h to 30 d. Clinical presentation for these patients were non-specific. Diagnosis was made mainly by computed tomography scan. Most of the patients were managed non-operatively with bowel rest and intravenous antibiotics.

Research conclusions

The entity of post-colonoscopy diverticulitis remains debatable due to the variable timeframe included following colonoscopy in the literature. Regardless of whether this is a true complication post-colonoscopy or a *de novo* event, early diagnosis is vital to guide appropriate treatment.

Research perspectives

The results of this systematic review should inform future prospective studies especially registries to record this as a potential complication following colonoscopy to further understand its true incidence and risk factors.

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CASE REPORT

Endoscopic treatment of blue rubber bleb nevus syndrome in a 4-year-old girl with long-term follow-up: A case report

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Abstract

BACKGROUND

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular disease, difficult to diagnose and choose a treatment method, especially in young children. There are several limiting factors to the use of enteroscopy for diagnostics and treatment in pediatric patients, in general. The literature on BRBNS cases is limited and presents various therapeutic approaches.

CASE SUMMARY

We present here a case of BRBNS involving a 4-year-old female, whose intestinal venous lesions were successfully treated by endoscopic sclerotherapy and aethoxysklerol foam. Skin lesions, typical for BRBNS, appeared on the 8th d of the child's life and their number increased over the next several months. The child also experienced episodes of critical decrease in hemoglobin level (by as much as 52 g/L) for several years, requiring iron supplementation and several blood transfusions. Video capsule endoscopy revealed numerous vascular formations in the small bowel. The combined findings of gastrointestinal venous formations and skin lesions prompted BRBNS diagnosis. Single-balloon enteroscopy was used to perform sclerotherapy, with aethoxysklerol foam. A positive effect was observed within 19 mo of follow-up. We continue to monitor the patient's hemoglobin level, every 2 wk, and it has remained satisfactory (> 120 g/L).

CONCLUSION

Endoscopic sclerotherapy can be effective in the clinical management of gastrointestinal manifestations of BRBNS in young children.

Sanfirau K and Svirsky A drafted and critically revised the manuscript for important intellectual content; Kolbik U contributed to drafting of the manuscript; Sautin A performed text structuring and critical revision of the manuscript for important intellectual content; Nikalayeva K drafted the manuscript and performed text structuring and critical revision of the manuscript; all authors gave final approval for the version to be published.

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Key Words: Blue rubber bleb nevus syndrome; Bean syndrome; Single-balloon enteroscopy; Children; Vascular malformations; Gastrointestinal tract; Sclerotherapy; Aethoxysklerol foam; Case report

Core Tip: In blue rubber bleb nevus syndrome (BRBNS), vascular malformations can affect any organ in the body but skin and gastrointestinal tract are the most frequent. Skin venous malformations have been observed in patients with BRBNS since childhood, with number and size of lesions increasing through time. Gastrointestinal lesions also occur at an early age and provoke gastrointestinal bleeding, leading to anemia. Treatment of the clinical manifestations of BRBNS can be carried out by endoscopic, pharmacological or surgical approaches. We present here a BRBNS case in a young child, treated by sclerotherapy with aethoxysklerol foam applied during single-balloon enteroscopy.

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INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS), or bean syndrome, is a rare congenital vascular disease, eliciting predominant damage of the skin and digestive tract[1,2] . The clinical spectrum of BRBNS is very heterogeneous, with various phenotypic patterns. Patients may experience single lesions of the skin and gastrointestinal (GI) tract or multiple lesions affecting the skin, GI tract, and other organs[3-5].

The pathogenesis of BRBNS has not been studied extensively. There is an assumption of autosomal dominant inheritance, based upon a change in the 9p chromosome locus and observations of this syndrome among blood relatives[6,7]; although, most cases appear to be sporadic[3,8].

Cutaneous venous formations are observed in 78% of patients and vascular lesions of the GI tract in 89%[9,10]. While BRBNS-related venous malformations can occur throughout the GI tract, they most often involve the small bowel (100%), followed by the colon (74%) and the stomach (26%); they vary in shape and number, ranging from a few to several hundred lesions[8,11] . The development of BRBNS is associated with GI bleeding, and normally the lesions grow in number and size over the lifetime of an afflicted individual[12]. The skin lesions rarely cause serious clinical problems-in contrast to the GI vascular malformations, which can cause acute or chronic bleeding and subsequent anemia, and in some cases fatality[13,14].

We present, herein, a case of BRBNS in a 4-year-old female with skin and GI manifestations.

CASE PRESENTATION

Chief complaints

A 4-year-old female was hospitalized in the Republican Center of Pediatric Surgery (Minsk, Belarus) in 2017 with the signs of chronic GI bleeding, iron deficiency anemia, episodes of melena, and a rapid deterioration in her general condition.

History of present illness

During the first year of observation in our clinic, the child underwent seven procedures of blood transfusions due to low hemoglobin levels before the first sclerotherapy was performed.

Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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History of past illness

The patient's birth (per *via* naturalis) had resulted from the mother's first pregnancy, which was also full-term. Her birth weight was 3760 g and length was 51 cm. The patient's mother noticed a roundish dark blue, soft-elastic formation on the skin of the child's thigh at 8 d after the birth. A few months later, new formations appeared on the skin of the child's head (at the border of the forehead and parietal ridge) and lumbar, perianal and plantar areas.

Anamnesis vitae yielded report of venous malformations involving the gluteo-femoral region, which had been partly excised at the age of 3 mo. Several complaints of melena were also disclosed. In addition, the parents reported that, at the age of 2 years, the child had developed periodic lethargy, drowsiness, and pallor of the skin; clinical assessment at that time yielded the first detection of a significant decrease in hemoglobin levels. Thus, iron supplements were prescribed. Several other episodes of a critical decrease in hemoglobin reportedly occurred over the next few years, all of which required a blood transfusion.

Personal and family history

The patient has no family history of BRBNS.

Physical examination

The patient's skin showed an overall paleness and several vascular skin lesions were found in the lumbar region, the inner part of the left thigh, the lower leg, the forearm (Figure 1), and on the sole of the right foot. The formations were of various sizes but all had a soft, elastic-like consistency and showed a cyanotic coloration.

Laboratory examinations

The patient's blood parameters were low, with hemoglobin of 95 g/L (normal range: 110-140 g/L), mean corpuscular hemoglobin concentration of 32.8 (normal range: 31.9-35.6 g/dL), erythrocytes of 4.4 × 10^{12}/L (normal range: 3.9-5.3 × 10^{12}/L), and hematocrit of 29% (normal range: 34%-40%).

Imaging examinations

Ultrasound showed vascular malformations in the left lobe of the liver, pancreas, bladder, and left ovary. Magnetic resonance imaging of the soft tissues of the lower extremities showed vascular malformations in the upper third of the left thigh. Although gastroscopy and colonoscopy were unsuccessful in detecting the source of GI bleeding, capsule enteroscopy revealed multiple (-10) vascular formations in the wall of the small intestine (Figure 2). All formations appeared round in shape and bluish-purple in color; the largest reached 2 cm in diameter.

FINAL DIAGNOSIS

BRBNS with secondary severe iron deficiency anemia.

TREATMENT

Sclerotherapy was ordered *via* single-balloon enteroscopy (Figure 3). During the first attempt at antegrade enteroscopy, it became clear that a total examination of the small bowel would be technically impossible. Therefore, subsequent enteroscopies were carried out with sequential antegrade and retrograde access guided by a tattoo of the maximum antegrade passage area of the enteroscope and simultaneous sclerotherapy. From December 2017 to March 2020, five total single-balloon enteroscopies were performed (Table 1). During each, foam sclerotherapy was carried out using 10 mL of a 1% aethoxysklerol solution, targeting all of the vascular malformations that had been identified. The sclerotherapy procedure itself was performed according to the Tessari method[15], in which a 1:4 mixture of the sclerosing agent and air [2 mL of 1% aethoxysklerol (10 mg/mL) mixed with 8 mL of air] was pumped in *via* two syringes connected by a 3-way adapter with a tap.

Table 1 Characteristics of the patient's enteroscopies and spread of vascular malformations

	December 20, 2017	March 23, 2018	May 22, 2018	August 31, 2018	March 30, 2020
Enteroscopy					
Antegrade	+	+	+	+	+
Retrograde	-	+	+	+	+
Sclerotherapy	+	+	+	+	+
Malformations					
Stomach	-	+	+ (sclerotherapy)	No new ones	Not visualized
Small bowel	+	+	+	+	+
Large bowel	-	-	-	-	+

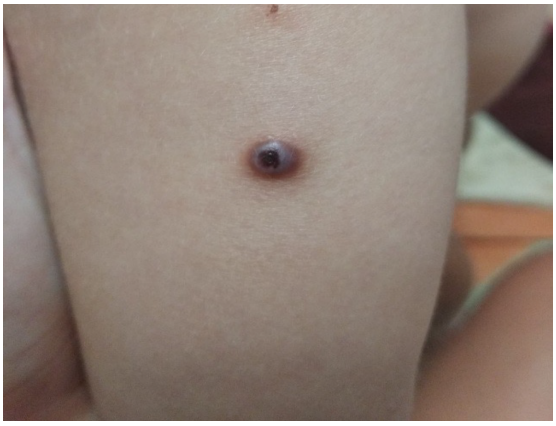

Figure 1 Vascular malformations on the patient's forearm.

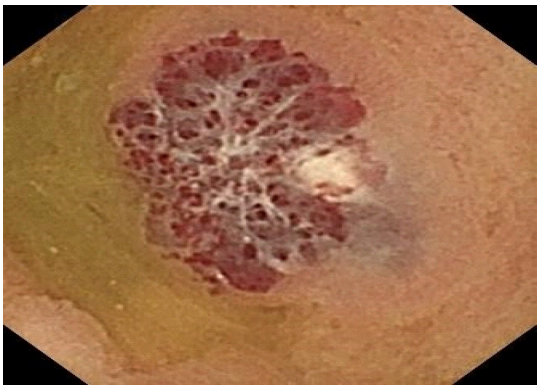

Figure 2 Capsule endoscopy revealed a large vascular formation in the wall of the small bowel.

OUTCOME AND FOLLOW-UP

The total follow-up duration was 33 mo (from December 2017 to September 2020). The first period of remission lasted 15 mo (from October 2018, upon the first detection of hemoglobin > 120 g/L, to January 2020). In February 2020, the patient's hemoglobin level began to fall, reaching a low of 97 g/L in March 2020. At the end of March 2020, single-balloon enteroscopy was reperformed. New vascular malformations were detected in the small bowel and, for the first time, in the colon, and these were considered as the likely cause of the hemoglobin decline. The sequential sclerotherapy was followed by a return of the hemoglobin level to the previous value of 120 g/L in early May 2020. The 2-wk interval follow-ups have shown the level to remain at > 120 g/L since then (Figure 4). It's worth noting that the child has not received iron supplement therapy since November 2018.

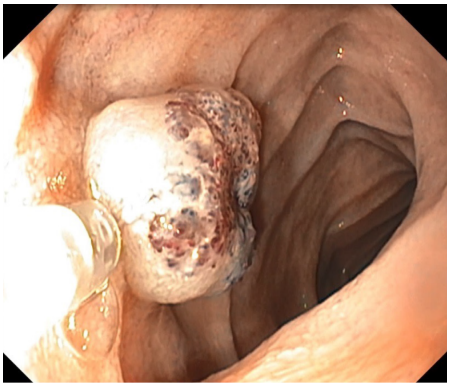

Figure 3 Intraoperative view of sclerotherapy of the vascular formation in the small bowel.

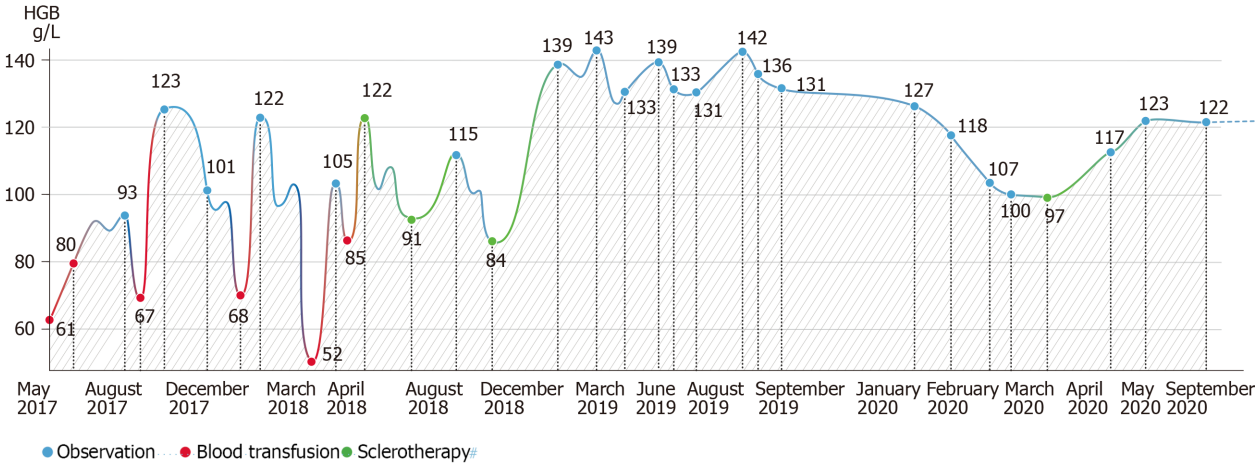

Figure 4 Hemoglobin level dynamics depend on blood transfusions and foam sclerotherapy of venous malformations and follow-up.

DISCUSSION

Treatment of BRBNS is usually based upon the patient's symptomatic profile and depending on degree of GI damage and/or involvement of other organs in the pathological process[10,16]. Choosing the optimal therapy for the manifestation of BRBNS with GI bleeding is a rather difficult task, especially when it comes to a 4-year-old patient. On the one hand, balloon-assisted enteroscopy-while being the gold standard for the diagnosis and treatment of bowel malformations in adult patients with BRBNS-is a relatively unsafe method in young children[17]. Limiting factors in any case are age and weight, especially so for children. Thus, we turned to the literature on pediatric cases of BRBNS.

Chen *et al*[18] reported on the successful performance of two-balloon enteroscopy in 72 pediatric patients, the youngest of whom was 6 years of age. In addition, Isoldi *et al*[10] reported on 18 clinical cases of BRBNS in children; all 4 who underwent balloon-assisted enteroscopy experienced a positive effect that lasted for 4-16 mo. We also chose to treat our patient's illness with balloon-assisted (single) enteroscopies, and the beneficial clinical effect on hemoglobin endured over a total of 19 mo [from October 2018 to September 2020, excepting the 3 mo (February-April 2020) before the last treatment].

Different kinds of GI malformations in BRBNS can be addressed by surgical treatment; although, this approach is rather aggressive, carries risk of postoperative complications, and is probably better justified for patients with few GI malformations located in a limited span of the bowel. There is also the risk of re-manifestation after resection[19], even for the combination method of endoscopic electrocoagulation and surgical removal[20]. The endoscopic interventions themselves, including argon plasma coagulation, electrocautery and histoacryl injection, also carry risk of perforation and rebleeding[11,21]. In our case, the venous malformations detected during enteroscopy numbered more than 15 and were located along the entire length of the hollow organs

of the GI tract. This situation would have required particularly extensive laparoscopic/open resection, posing too great overall risk to the young child. Moreover, the child's young age presented the risk of new lesions forming on the wall of the intestine during the subsequent years of life, adding further reason against the laparoscopic/open resection approach[8] . Endoscopic sclerotherapy was suggested as a less aggressive and less invasive option.

Two studies[15,22] in the literature have suggested systemic medical therapy with sirolimus as highly effective for pediatric patients. Unfortunately, two other studies[23,24] confounded the potential benefit by reporting on substantial negative side effects.

CONCLUSION

The applied method of endoscopic treatment showed its effectiveness in regard to rescue of hemoglobin level for 19 mo, during a 3-year follow-up period. New, clinically significant malformations appeared in the patient's small bowel only at 16 mo after the first application of endoscopic sclerotherapy. In the Republic of Belarus, the patient described herein is, to date, the smallest patient by age and weight to undergo total single-balloon enteroscopy. There were no side effects related to the procedure in our case. Thus, endoscopic sclerotherapy with aethoxysklerol foam can be an appropriate option for BRNBS treatment, even in young children.

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