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Clostridium septicum foot gangrene associated with colorectal cancer

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Abstract

INTRODUCTION: Since the second half of the 20th century, an association between the occurrence of Clostridium septicum and Streptococcus gallolyticus infections in patients with colorectal cancer has been described in specialist literature. Infections are manifested by bacteremia, septic embolism, cellulitis, myonecrosis, and gas gangrene of the limbs.

MATERIAL AND METHODS: The authors present a case of a rare association between lower limb gangrene caused by the septic embolization of a Clostridium septicum infection and malignancy of colon ascendens in a polymorbid patient. Gangrene of the lower limb led to septic shock requiring acute amputation treatment. After managing the acute condition, the patient was operated on for a malignant colon tumour.

DISCUSSION: The process of carcinogenesis often takes years and is almost asymptomatic. The occurrence of S. bovis/S. equinus (SBSEC) and C. septicum bacteremia, respectively, is relatively rare, but their presence is often associated with the occurrence of malignancy, most often of the lower gastrointestinal tract. This paraneoplastic symptom may be the first manifestation of a malignant disease. The effect of exotoxins can lead to sepsis or even septic shock with a mortality of 48-56%..

CONCLUSION: Clostridium septicum and Streptococcus gallolyticus infections are rare in clinical practice. However, their presence can be a first paraneoplastic symptom, and therefore the doctor should look for a possible oncological disease when they are detected. The main diagnostic methods include colonoscopy and imaging, especially CT scan.

CASE REPORT

INTRODUCTION

Colorectal cancer is one of the three most common cancers worldwide, and accurate diagnosis and successful treatment should be a priority for any healthcare system. Genetic and environmental factors play a role in the etiology, and the influence of the intestinal microbiome is currently being demonstrated (Torre *et al.* 2015; Kwong *et al.* 2018). The association between intestinal microbioma disorder and increased colorectal cancer (CRC) has long been pointed out (Sobhani *et al.* 2011). Bacteria can play a significant role in carcinogenesis with the gradual development of CRC. Significant associations between CRC and bloodstream infections caused by Streptococcus gallolyticus, Clostridium septicum, Bacteroides fragilis, Fusobacterium nucleatum, Peptostreptococcus species and some other bacteria are known (Jans *et al.* 2015).

The proinflammatory effects of bacteria are applied to the pathomechanism of tumour formation by modulating the E-cadherin and b-catenin signaling pathways that activate downstream proinflammatory responses. Streptococcus bovis activates interleukin 8 (IL-8) to form hyper-proliferative and aberrant colonic crypt formation in a mouse model. In addition to the oncogenetic potential of bacteria, bacteremia is also observed as a result of the passage of viable bacteria through the destroyed intestinal wall caused by the tumorous process. The subsequent spread of bacteria can cause infection in any part of the body, including septic limb embolization (Biarc *et al.* 2004).

CASE REPORT

The 86-year-old polymorbid patient (ischemic heart disease, arterial hypertension, condition after right breast ablation for Paget's disease) was acutely admitted to the Department of Infectious Diseases at Martin University Hospital for a septic condition. At the initial examination, she reported problems with the left lower limb that had lasted for about 24 hours - a gradual swelling of the foot with increasing pain. On the skin of the affected limb, color changes were visible with a transition to purple. There were superficial erosions on the ankle and dorsum of the foot, and there was a phlegmon with edema in the hallux area (Fig. 1).

Massive leukocytosis (76.5x10^9/l), moderate anemia (96 g/l) and severe thrombocytopenia (42x10^9/l) were present in the blood count. The value of C-reactive protein (CRP) was 168 mg/l and presepsin 391 ng/l. The patient had mineral imbalance with hyponatremia (132 mmol/l) and hypokalemia (2.5 mmol/l). Coagulation disorder was also found (INR 1.6). The SOFA score reached 6 points and the APACHE II score was 15 points. The RT-PCR assay for COVID-19 was negative.

Initial therapy included parenteral rehydration and empirical antibiotic therapy (Ampicillin + Sulbactam, Clindamycin, Metronidazole). CT angiography of the lower extremities did not show hemodynamically significant stenoses of the arterial system. Tissue edema and gas bubbles around the head of the first metatarsus were present on the left foot (Fig. 2). The plantar artery did not appear on the affected limb. The patient was examined by a vascular surgeon who presupposed peripheral embolization with a septic embolus with the subsequent development of a septic condition.

The next day, the local finding on the left lower limb worsened; the movement of the foot was minimal, and the sensitivity in the acral part of the limb disappeared. An elevation of inflammatory parameters occurred in the laboratory tests (leukocytes 84.3x10^9/l; CRP 295 mg/l; procalcitonin 48.1 μg/l). The septic condition progressed to septic shock with the need to support the circulation of norepinephrine. In addition, the SOFA score reached 9 points and APACHE II remained at 15 points. The patient was examined by a surgeon who indicated an urgent amputation of the foot in the Lisfranc joint. The amputation wound was left open, without sutures. The patient was hospitalized postoperatively at the surgical ICU.

On the first postoperative day after amputation, epidermolysis, edema and phlegmon of the limb above the knee developed. High inflammatory activity persisted in the laboratory tests. The surgeon therefore indicated a high amputation at thigh level. The wound was primarily sutured. Already a few hours after reamputation, the clinical condition of the patient with circulatory stabilization improved significantly without the need for norepinephrine. Inflammatory parameters were falling sharply. The amputation wound healed in primary intention.

Microbiological examination of the swab from the amputation wound as well as from the blood culture confirmed the presence of Clostridium septicum, which was sensitive to the administered antibiotics.

In addition to the underlying disease, the original CT scan revealed a thickening of the colon wall or a tumour of unknown origin in the ascending colon with regional lymphadenopathy (Fig. 3). After stabilization of the patient, a colonoscopic examination was completed, which revealed a tumour in the suspected area. Histological examination confirmed conventional adenocarcinoma, which had been clinically asymptomatic until then. The first manifestation of colon cancer was the paraneoplastic gangrene of the left leg caused by the bacterium Clostridium septicum.

After a temporary hospitalization at the internal medicine clinic, the patient was admitted to the surgical clinic once again and laparoscopic right hemicolectomy with complete mesocolic excision was performed. The operation and postoperative courses were without complications and the patient was discharged on the 6th postoperative day.

Fig. 1. Clinical finding of the left foot

DISCUSSION

Historically, the first association between bacterial infection (endocarditis) and colorectal cancer began to be mentioned in the 1950s. Further findings gradually came during the following decades, when cases of bacterial endocarditis, soft tissue or limbs gas gangrene were described in patients with clinically unknown malignancy. These were patients with colorectal cancer, colon polyps, breast cancer or acute myeloblastic leukemia (Roses *et al.* 1974; Katlic *et al.* 1981; Satz *et al.* 1988). These bacteria with the mentioned association include in particular Clostridium septicum, Streptococcus gallolyticus subsp. gallolyticus, Clostridium perfringens, Fusobacterium nucleatum or Bacteroides fragillis (Kwong *et al.* 2018).

Prokaryote C. septicum was first isolated and described in 1877 thanks to the work of L. Pasteur and J. Joubert. Like C. perfringens, C. septicum are anaerobic, gram-positive and sporulating organisms (Shah *et al.* 2016). Clostridia are generally part of the normal intestinal flora of humans and we know more than 100 different strains of these bacteria; their importance in clinical practice varies considerably. They are most often associated with the term gas gangrene or myonecrosis. It is a life-threatening and rapidly progressing disease affecting the soft tissues of the limbs or other parts of the body. Its occurrence is often related to trauma and postoperative conditions; its severity is exacerbated by diabetes mellitus, immunosuppression, chronic renal failure and peripheral circulatory disorders. In 16% of cases, the infection occurs spontaneously - without an apparent external influence, and then C. septicum significantly predominates as the causative agent (Stevens & Bryant 2002; Perry & Floyd 2004; Sidhu *et al.* 2019). It is an opportunistic pathogen and produces several exotoxins. The alpha toxin degrades lecithin in cell membranes, creating hemolysis, thrombocytopenia and destruction of the blood supply, which provides better conditions for bacterial growth. Other exotoxins further contribute to myonecrosis and further spread of the pathogen (Shah *et al.* 2016). In the case of the transition to myonecrosis, mortality of up to 79 % within 48 hours of the onset of the problem has been reported in specialist literature (Dahmus *et al.* 2018). These properties of exotoxins explain the pathological mechanism of the origin and spread of foot gangrene in our patient, as well as the severe thrombocytopenia in the blood picture.

Compared to C. perfringens, which physicians may encounter more often, C. septicum is up to 300 times more virulent and also more resistant to the presence of oxygen. Due to these properties, it manifests itself much more often in healthy and adequately perfused tissues - clinically it occurs as a spontaneous gas gangrene (Prinssen *et al.* 1999). After tissue invasion, it causes ischemia and subsequent necrosis. The infection often affects areas that are supplied with blood by only one supply artery. The necrosis environment further supports the anaerobic metabolism of the pathogen, as well as the production of exotoxins. The accompanying feature is the formation of gas, which manifests clinically as crepitus during tissue palpation, or the gas bubbles presented in the soft tissues clearly visible in the CT pictures (Cullinane *et al.* 2017; Sidhu *et al.* 2019).

The unusual link with colorectal cancer lies in the local conditions located on the site of the tumour growth. The malignant process damages the surrounding intestinal mucosa, thus allowing the bacteria to enter the submucosa. Tumour metabolism, also in the form of anaerobic glycolysis, creates a more

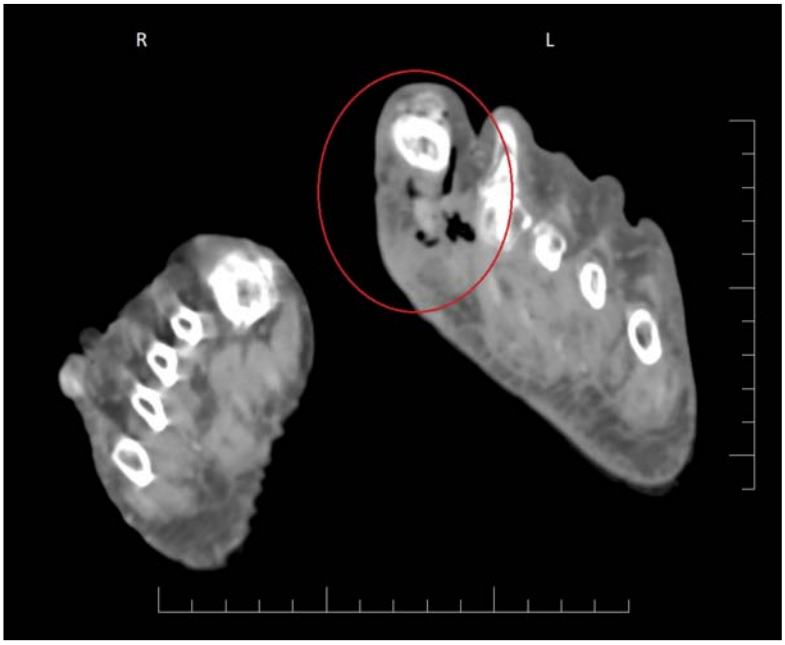

Fig. 2. CT scan of feet: edema and gas bubbles around the head of the first metatarsus of the left foot (red circle)

acidic and anaerobic environment that Clostridium can make good use of. Immunity failure that can still be highlighted by the administration of chemotherapy in the event of the treatment of malignancy helps Clostridium septicum to grow (Wentling *et al.* 2006; Shah *et al.* 2016). Associated malignancies are thus often more advanced forms of diseases that sufficiently disturb the intestine wall and allow the translocation of C. septicum. Interestingly, this association is present in 57% of cases of cecal carcinoma, while in general, cecal carcinomas develop in only 20% of all cases of colon cancer. Cecum represents the area with the lowest pH in the whole colon, which creates the best conditions for the growth of C. septicum (Dahmus *et al.* 2018).

In extremely rare cases, C. septicum infection may also be associated with small intestine malignancy. The first case described in this way dates from 1985 (Redington *et al.* 1985); another case was published by a team of authors in 2019. They described a 76-year-old woman with spontaneous myonecrosis of the left lower limb. Despite intensive therapy and surgical treatment, the patient died 7 days after the onset of symptoms. Before that, an exploratory laparotomy revealed an 11 cm tumour of the small intestine close to the ileo-cecal junction. Histologically, it was an invasive adeno-carcinoma (Saunders *et al.* 2019).

The association of these bacterial infections with malignancies is not common in clinical practice, which is also related to the generally low incidence

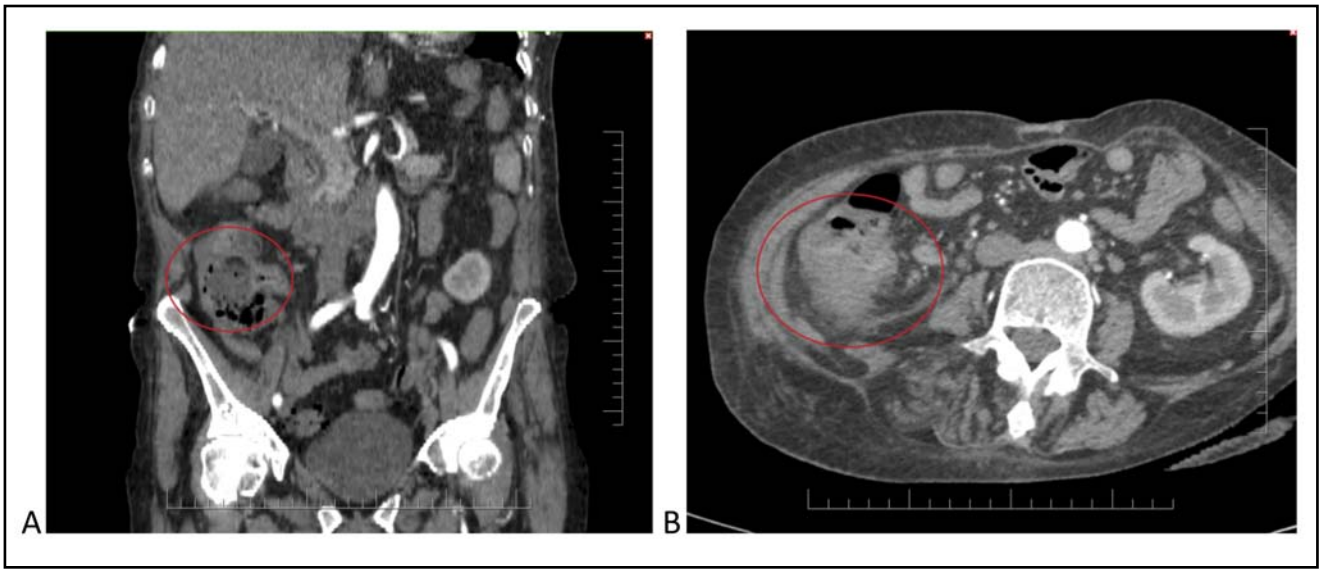

Fig. 3. Contrast-enhanced abdominal CT scan showing a tumour of the ascending colon (red circle): A) coronal projection; B) axial projection

Tab. 1. Incidence of malignancy in patients with C. septicum infection in available literature. (Percentages are rounded to whole numbers.)

Author and year of publication	Number of patients with infection	Number of patients with malignant tumour (%)
Alpern & Dowell 1969	28	23 (85%)
Pelfrey *et al.* 1984	8	7 (88%)
Bretzke *et al.* 1988	19	10 (53%)
Kornbluth *et al.* 1989	162	131 (81%)
Bodey *et al.* 1991	17	17 (100%)
Larson *et al.* 1995	32	16 (50%)
Chew *et al.* 2001	5	4 (80%)
Hermsen *et al.* 2008	231	185 (80%)
Mao *et al.* 2011	15	4 (27%)
Corredoira *et al.* 2017	44	32 (73%)

of infections caused by C. septicum. Larson *et al.* (1995) in his work, in which he collected data from 1966 to 1993, described that out of 241 cases of clostridial infections, only 32 could be attributed to C. septicum. However, up to 50% of patients with confirmed C. septicum infection had some form of malignancy. The other patients had at least signs of immunosuppression. Mortality among patients with C. septicum infection reached 56%. For these reasons, the authors recommend high caution and efforts to diagnose the presumed oncological disease. A slightly older study described 23 cases of malignancy (including 6 colorectal cancers) out of a total of 27 cases of C. septicum infection. Mortality reached 48%, with all cases of infection arising spontaneously from full health. The authors hypothesize the gastrointestinal tract as a source of infection for patients (Alpern & Dowell 1969). A substantially more recent work by Mao *et al.* (2011) describes 15 cases of C. septicum bacteraemia over a 4-year period. Colorectal cancer occurred in 4 patients. In this work, the authors recommend that diagnostic colonoscopy should be performed in all patients with C. septicum bacteremia, although other symptoms of intestinal malignancy may not be present. A more extensive study dates from 1989, in which the authors processed the available information and collected 162 cases of C. septicum infection. Malignancy was confirmed in 81% of patients: colorectal malignancy was confirmed in 34%, hematological malignancy affected 40%. The text of the thesis recommends increased vigilance in clinical practice, because in 37% of cases the malignancy was occult. The authors assume that the site of entry of the bacterium was the colonic mucosa. As mentioned above, the authors recommend a thorough search for possible malignancy (Kornbluth *et al.* 1989).

The largest sample of patients contains a study by Hermsen *et al.* (2008), in which the authors described 231 cases of C. septicum infection. Malignancies occurred in 185 patients and their overall survival rate was 48%. Of these, 98 cases of malignancy involved the gastrointestinal tract, 68 patients had a hematooncological malignancy, and 19 patients had a different malignancy. In the absence of malignancy, the mortality of the infection was not statistically affected and the incidence of diabetes mellitus did not affect patient survival. Surgical treatment of the infection significantly increased patient survival compared to conservative infection management (57% vs 26%).

There is another interesting multicenter study examining the association of C. septicum and the occurrence of CRC in the period 1988-2015. C. septicum infection was diagnosed in 44 patients (this represented 6.6 % of all Clostridial infections during this period). The malignant process occurred in 32 patients, of which CRC was present in 18 cases. Mortality within 30 days of hospitalization reached 47.7 %. Almost all deaths occurred in the first 48 hours (Corredoira *et al.* 2017). In 2020, Yamamoto *et al.* (2020) published a retrospective study examining 64,760 blood cultures from 2004-2018. The positivity of a particular Clostridial infection was in 40 blood samples, of which 37 patients had malignancy. The most common pathogen in the samples was C. perfringens, whereas C. septicum was detected in only two samples. Table 1 shows the incidence of malignant disease in patients with C. septicum infection in available literature.

Treatment of the above infection consists of an aggressive debridement of the affected tissues and combined ATB treatment, which must be administered intravenously. Broad-spectrum penicillins (eg piperacillin / tazobactam) in combination with nitroimidazoles (most commonly metronidazole) are recommended. Other possible preparations are e.g. clindamycin, cefoxitin, ampicillin / sulbactam or carbapenems. The duration of treatment is a matter of debate. Usually, the need for further treatment ceases in a hemodynamically stable patient who no longer

Tab. 2. Current SBSEC nomenclature compared to the original designation (Schlegel *et al.* 2003; Whiley *et al.* 2009)

Original designation	Biotype classification	Recommended terminology
S. alactolyticus	Variable	*S. alactolyticus*
S. bovis	Biotype I.	*S. gallolyticus subsp. gallolyticus*
	Biotype II.1	*S. infantarius subsp. infantarius*
		S. lutetiensis
	Biotype II.2	*S. gallolyticus subsp. pasteurianus*
S. equinus	Predominantly biotype II.2	*S. equinus*
S. macedonicus	Probably biotype II.1	*S. gallolyticus subsp. macedonicus*

requires additional surgical debridement (Nanjappa *et al.* 2015; Cullinane *et al.* 2017).

The pathogen, formerly known as Streptococcus bovis due to the knowledge of molecular genetics, belongs now, together with other bacteria, to the S. bovis / S. equinus complex (SBSEC). This complex represents a group of non-β-hemolytic streptococci, often colonizing domesticated animals such as cattle or horses. We are currently describing 7 subspecies in the complex (Table 2), and they have gained the attention of experts due to their role in the development of infectious endocarditis, and some of its members also have a strong association with colorectal cancer (Jans *et al.* 2015).

All SBSEC members are catalase negative, oxidase negative, immobile, non-sporulating, gram-positive prokaryotes, which usually grow in pairs or chains consisting of individual cocci. S. gallolyticus subsp. gallolyticus is found in the digestive tract of 2.5-15% of the population according to older data (Schlegel *et al.* 2003; Pasquereau-Kotula *et al.* 2018). However, its true incidence in the population may be significantly higher; a recent German study of 99 healthy volunteers using real-time PCR showed the presence of bacteria in the stool in 62.5% of the total number of volunteers (Dumke *et al.* 2017).

Bacteremia and subsequent infectious endocarditis are the two main clinical manifestations of SBSEC infection. The bacterium is usually diagnosed from blood cultures and is often a manifestation of endocardial infection, ongoing meningitis, or occult colorectal cancer. In particular, the presence of bacteremia in the above-mentioned S. gallolyticus subsp. gallolyticus has a strong correlation with the incidence of infectious endocarditis. The presence of malignancy on the colonic mucosa was present in 67% of the examined samples of 68 patients with bacteremia of this streptococcus. SBSEC infection usually affects the elderly in the 6th decade and above (Ruoff *et al.* 1989). In a multicenter study by Corredoira *et al.* the incidence of colon cancer in infections with S. gallolyticus subsp. gallolyticus was investigated. A total of 257 such infections have been diagnosed, of which 192 affected the endocardium. The occurrence of the malignant process was proven in 50 patients and the total 30-day mortality rate was 9.7% (Corredoira *et al.* 2017).

An extensive review article by Abdulamir *et al.* states that S. gallolyticus can be pro-oncogenic and helps precancerous lesions to transition to malignancy. The production of NF-κB and IL-8, which promotes carcinogenesis and angiogenesis in the colonic mucosa, plays an important role here. Furthermore, according to the authors, the bacterium can directly colonize tumour tissues, which triggers an inflammatory response that also promotes gradual oncogenesis. It can benefit from metabolites produced by tumour cells and consequently significantly reduce other bacterial flora around the tumour with its bacterial toxins. It is not the primary trigger of oncogenesis, but serves as a factor accelerating the development of cancer from pre-malignant lesions (Abdulamir *et al.* 2011).

In a paper by Kwong *et al.* (2018), the authors point out chronic mucositis as an important factor in the development of colorectal cancer. S. galllolyticus antigens stimulate the production of several cytokines: tumour necrosis factor α, IL-1β, IL-6 and IL-8. They promote vasodilation, increase capillary permeability, and are thought to allow better penetration into the bloodstream and subsequent bacteremia. Theoretically, this mechanism can be expected already during the formation of adenomas (premalignant lesions), which causes bacteremia at an early stage of carcinogenesis and thus increases the chances of an early diagnosis of the lesion. The authors describe an increased incidence of colorectal cancer in patients with S. gallolyticus, Bacteroides fragillis, C. septicum, C. perfringens or Fusobacterium nucleatum. At the end of their work, the authors recommend the thorough monitoring and diagnosis of potential lesions in patients with bacteremia caused by these pathogens.

A meta-analysis by Boleij *et al.* states that S. gallolyticus subsp. gallolyticus is the only subspecies of S. bovis to have a strong association with colorectal cancer. Bacterial DNA was found in 49% of tumour samples and only 8% of healthy colonic mucosa samples, and the antibody response was also more pronounced in patients with colorectal malignancy. Asymptomatic individuals with this malignancy had

blood cultures positive for the presence of S. gallolyticus subsp. gallolyticus. The authors recommend the possibility of using patient screening for its presence in the future, for example using molecular genetic methods such as PCR. Further carefully-designed studies are also needed, which will use intensive and endoscopic methods to evaluate the local findings of the studied patients. The aim is to reveal the exact links between the various stages of colorectal cancer and the incidence of colonization / infection (Boleij *et al.* 2011; Paritsky *et al.* 2015).

Due to the strong association of S. gallolyticus subsp. gallolyticus and colorectal cancer, colonoscopy of the entire intestine is recommended in patients who have been infected with this bacterium. In future research, it will be useful to examine the relationship between this pathogen and the host's immune system (Pasquereau-Kotula *et al.* 2018).

CONCLUSION

Recent findings indicate that not only the environment and genetics but also the gut microbiome play an important role in the pathogenesis of the colon lesion. The process of carcinogenesis often takes years and is almost asymptomatic. The occurrence of SBSEC and C. septicum bacteremia, respectively, is relatively rare, but their presence is often associated with the occurrence of malignancy, most often in the lower digestive tract. When they are detected, the doctor should look for a possible oncological disease. The main diagnostic methods include colonoscopy and imaging, especially CT-scan.

REFERENCES

1 Abdulamir AS, Hafidh RR, Abu Bakar F (2011). The association of Streptococcus bovis/gallolyticus with colorectal tumors: the nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res. **30**(1): 11.
2 Alpern RJ, Dowell VR Jr (1969). Clostridium septicum infections and malignancy. JAMA. **209**(3): 385–388.
3 Biarc J, Nguyen IS, Pini A, Gossé F, Richert S, Thiersé D, Van Dorsselaer A, Leize-Wagner E, Raul F, Klein JP, Schöller-Guinard M (2004). Carcinogenic properties of proteins with pro-inflammatory activity from Streptococcus infantarius (formerly S. bovis). Carcinogenesis. **25**(8): 1477–84.
4 Bodey GP, Rodriguez S, Fainstein V, Elting LS (1991). Clostridial bacteremia in cancer patients. A 12-year experience. Cancer. **67**(7): 1928–1942.
5 Boleij A, van Gelder MM, Swinkels DW, Tjalsma H (2011). Clinical Importance of Streptococcus gallolyticus infection among colorectal cancer patients: systematic review and meta-analysis. Clin Infect Dis. **53**(9): 870–878.
6 Bretzke ML, Bubrick MP, Hitchcock CR (1988). Diffuse spreading Clostridium septicum infection, malignant disease and immune suppression. Surg Gynecol Obstet. **2166**(3): 197–199.
7 Chew SS, Lubowski DZ (2001). Clostridium septicum and malignancy. ANZ J Surg. **71**(11): 647–649.
8 Corredoira J, Grau I, Garcia-Rodriguez JF, García-País MJ, Rabuñal R, Ardanuy C, García-Garrote F, Coira A, Alonso MP, Boleij A, Pallares R (2017). Colorectal neoplasm in cases of Clostridium septicum and Streptococcus gallolyticus subsp. gallolyticus bacteraemia. Eur J Intern Med. **41**: 68–73.
9 Cullinane C, Earley H, Tormey S (2017). Deadly combination: Clostridium septicum and colorectal malignancy. BMJ Case Rep. **2017**: bcr2017222759.
10 Dahmus JD, Kotler DL, Kastenberg DM, Kistler CA (2018). The gut microbiome and colorectal cancer: a review of bacterial pathogenesis. J Gastrointest Oncol. **9**(4): 769–777.
11 Dumke J, Vollmer T, Akkermann O, Knabbe C, Dreier J (2017). Case-control study: Determination of potential risk factors for the colonization of healthy volunteers with Streptococcus gallolyticus subsp. gallolyticus. PLoS One. **12**(5): e0176515.
12 Hermsen JL, Schurr MJ, Kudsk KA, Faucher LD (2008). Phenotyping Clostridium septicum infection: a surgeon's infectious disease. J Surg Res. **148**(1): 67–76.
13 Jans C, Meile L, Lacroix C, Stevens MJ (2015). Genomics, evolution, and molecular epidemiology of the Streptococcus bovis/Streptococcus equinus complex (SBSEC). Infect Genet Evol. **33**: 419–436.
14 Katlic MR, Derkac WM, Coleman WS (1981). Clostridium septicum infection and malignancy. Ann Surg. **193**(3): 361–364.
15 Kornbluth AA, Danzig JB, Bernstein LH (1989). Clostridium septicum infection and associated malignancy. Report of 2 cases and review of the literature. Medicine (Baltimore). **68**(1): 30–37.
16 Kwong TNY, Wang X, Nakatsu G, Chow TC, Tipoe T, Dai RZW, Tsoi KKK, Wong MCS, Tse G, Chan MTV, Chan FKL, Ng SC, Wu JCY, Wu WKK, Yu J, Sung JJY, Wong SH (2018). Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer. Gastroenterology. **155**(2): 383–390.e8.
17 Larson CM, Bubrick MP, Jacobs DM, West MA (1995). Malignancy, mortality, and medicosurgical management of Clostridium septicum infection. Surgery. **118**(4): 592–7; discussion 597–8.
18 Mao E, Clements A, Feller E (2011). Clostridium septicum Sepsis and Colon Carcinoma: Report of 4 Cases. Case Rep Med. **2011**: 248453.
19 Nanjappa S, Shah S, Pabbathi S (2015). Clostridium septicum Gas Gangrene in Colon Cancer: Importance of Early Diagnosis. Case Rep Infect Dis. **2015**: 694247.
20 Paritsky M, Pastukh N, Brodsky D, Isakovich N, Peretz A (2015). Association of Streptococcus bovis presence in colonic content with advanced colonic lesion. World J Gastroenterol. **21**(18): 5663–5667.
21 Pasquereau-Kotula E, Martins M, Aymeric L, Dramsi S (2018). Significance of Streptococcus gallolyticus subsp. gallolyticus Association with Colorectal Cancer. Front Microbiol. **9**: 614.
22 Pelfrey TM, Turk RP, Peoples JB, Elliott DW (1984). Surgical aspects of Clostridium septicum septicemia. Arch Surg. **119**(5): 546–550.
23 Perry BN, Floyd WE 3rd (2004). Gas gangrene and necrotizing fasciitis in the upper extremity. J Surg Orthop Adv. **13**(2): 57–68.
24 Prinssen HM, Hoekman K, Burger CW (1999). Clostridium septicum myonecrosis and ovarian cancer: a case report and review of literature. Gynecol Oncol. **72**(1): 116–119.
25 Redington AN, Spring R, Batten JC (1985). Adenocarcinoma of the ileum presenting as non-traumatic clostridial myonecrosis in cystic fibrosis. Br Med J (Clin Res Ed). **290**(6485): 1871–2.
26 Roses DF, Richman H, Localio SA (1974). Bacterial endocarditis associated with colorectal carcinoma. Ann Surg. **179**(2): 190–1.
27 Ruoff KL, Miller SI, Garner CV, Ferraro MJ, Calderwood SB (1989). Bacteremia with Streptococcus bovis and Streptococcus salivarius: clinical correlates of more accurate identification of isolates. J Clin Microbiol. **27**(2): 305–308.
28 Satz N, Bertschinger P, Ott A, Knoblauch M (1988). Streptococcus-bovis-Bakteriämie und Kolonerkrankungen [Streptococcus bovis bacteremia and colonic diseases]. Dtsch Med Wochenschr. **113**(22): 889–91.
29 Saunders RN, Hayakawa E, Gibson CJ, Chapman AJ (2019). Clostridium septicum Myonecrosis Secondary to an Occult Small Bowel Adenocarcinoma. J Gastrointest Cancer. **50**(4): 1001–1004.
30 Schlegel L, Grimont F, Ageron E, Grimont PAD, Bouvet A. Reappraisal of the taxonomy of the Streptococcus bovis/Streptococcus equinus complex and related species: description of Streptococcus gallolyticus subsp. gallolyticus subsp. nov., S. gallolyticus subsp. macedonicus subsp. nov. and S. gallolyticus subsp. pasteurianus subsp. nov. Int J Syst Evol Microbiol. **53**(Pt 3): 631–645.
31 Shah S, Nanjappa S, Pabbathi S, Greene J (2016). Clostridium septicum Case Series. Infectious Diseases in Clinical Practice. **24**(2): 72–75.

32 Sidhu JS, Mandal A, Virk J, Gayam V (2019). Early Detection of Colon Cancer Following Incidental Finding of Clostridium septicum Bacteremia. J Investig Med High Impact Case Rep. **7**: 2324709619832050.
33 Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, Corthier G, Tran Van Nhieu J, Furet JP (2011). Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One. **6**(1): e16393.
34 Stevens DL, Bryant AE (2002). The role of clostridial toxins in the pathogenesis of gas gangrene. Clin Infect Dis. **35**(Suppl 1): S93–S100.
35 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015). Global cancer statistics, 2012. CA Cancer J Clin. **65**(2): 87–108.
36 Wentling GK, Metzger PP, Dozois EJ, Chua HK, Krishna M (2006). Unusual bacterial infections and colorectal carcinoma--Streptococcus bovis and Clostridium septicum: report of three cases. Dis Colon Rectum. **49**(8): 1223–1227.
37 Whiley RA, Hardie JM (2009). Genus I. Streptococcus. In: Holt J, Garrity G, Boone D, editors. Bergey's manual of systematic bacteriology: The firmicutes, 2nd edition. New York: Springer. p. 655–711.
38 Yamamoto Y, Itoh N, Sugiyama T, Kurai H (2020). Clinical features of Clostridium bacteremia in cancer patients: A case series review. J Infect Chemother. **26**(1): 92–94.