Liver Abscess due to *Streptococcus intermedius* Bacteremia and Its Association with Colonic Carcinoma: Is Bacteremia with *Streptococcus intermedius* an Alert for Colonic Carcinoma?

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**Keywords**

Abscess · Colon cancer · Intussusception · Liver · *Streptococcus*

**Abstract**

Liver abscess caused by some kinds of *Streptococcus* group such as *Streptococcus bovis* group has been recognized to associate with colorectal cancer. *Streptococcus milleri* group with liver abscess has not been received much attention in this point of view. Here, we report the case of a 63-year-old man who developed liver abscess with *S. intermedius*, which belongs to the *S. milleri* group. We confirmed that this case was accompanied by cecal carcinoma by colonoscopy. The tumor was a pathological lead point of intussusception of cecum. On the 26th day, open right hemicolectomy was performed. In this case, bacterial endophthalmitis was a complication due to bacteremia. The patient underwent ophthalmic surgery on the 98th day. Research investigating 16S rRNA of the mucosal colon microbiome reported that the *S. intermedius* gene was upregulated in patients with colorectal carcinoma. It is recommended that liver abscess with *S. intermedius* bacteremia should alert the clinician about the risks of carcinoma of the colon and abscess formation in distant organs. We here list the case reports of...
liver abscess caused by *Streptococcus* other than *S. bovis* group, which was associated with colonic carcinoma, and suggest the need for further research about *S. milleri* group.

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**Introduction**

Pyogenic liver abscesses, which can be life-threatening, are mainly caused by Gram-negative rods, such as *Escherichia coli* or *Klebsiella pneumoniae*. One of the most invasive groups of bacteria for liver abscess is the *Streptococcus* genus. In addition to the pyogenic potential of the *Streptococcus*, some of group of *Streptococcus* have a role of warning sign of colonic carcinoma with liver abscess. The association between liver abscess with *Streptococcus bovis* bacteremia and colonic carcinoma has been well described and well known [1]. However, other groups of *Streptococcus* have not been received much attention in this point of view. *Streptococcus intermedius* is not a common causative agent of liver abscess but has been recognized for its unique pathophysiological and clinical features. Here, we report a case of pyogenic liver abscess with *S. intermedius* bacteremia. This case was accompanied by intussusception of the colon, of which cecal carcinoma was the leading point. We discuss this case focusing on the potential relevance of carcinoma of the colon and bacteremia caused by *S. milleri* group including *S. intermedius*, which tends to cause distant abscesses, including in the liver.

**Case Report/Case Presentation**

A 63-year-old man with fever and productive cough visited a local clinic. Three days after the visit, the patient developed diarrhea and fever with shivering. A week after the initial visit, his condition worsened, and he was referred to our hospital via a municipal hospital for suspected sepsis and organ failure.

Although the patient had a history of bronchial asthma, he had no history of diabetes mellitus, alcohol abuse, or liver disease. Initial vital signs in the emergency room were as follows: body temperature 38.1°C, blood pressure 114/62 mm Hg, heart rate 102 beats/min, respiratory rate 30/min, and oxygen saturation 97% in room air. Abdominal examination revealed tenderness and pain from the right costal region to the epigastric region.

Laboratory blood examination revealed that C-reactive protein and procalcitonin (>100 ng/mL, normal range <0.05 ng/mL) levels increased remarkably, demonstrating a marked inflammatory response (Table 1). In addition to decreased platelet count, extended prothrombin time, increased D-dimer level, and decreased antithrombin III concentration, which was 53% of standard value, suggested the beginning of disseminated intravascular dissemination. Biochemical examination revealed jaundice and elevated hepatobiliary enzyme levels. Impaired renal function was also demonstrated by elevated creatinine and blood urea nitrogen levels (Table 1).

Computed tomography of the abdomen showed hepatomegaly with a low-density mass in the right lobe of the liver, suggesting the presence of a liver abscess. Thickening of the cecum wall suggested the presence of a soft tissue mass, which was confirmed as a malignant tumor later (Fig. 1).

Abdominal sonography also revealed abscess formation in S7 of the right lobe of the liver, approximately 70 × 40 mm in diameter, with indistinct internal heterogeneity. Percutaneous
drainage was not performed considering the progression of disseminated intravascular coagulation. Biliary sludge was present in the gallbladder, but there were no signs of cholecystitis (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526158).

Focused sonography of the heart showed no obvious valvular dysfunction or verrucous adhesion, although left ventricular systolic function was slightly decreased (left ventricular ejection fraction, 57.1%; fractional shortening, 30.2%).

Treatment, started with antimicrobial agents of meropenem (0.5 g) three times a day and metronidazole (0.5 g) three times a day on the diagnosis of the liver abscess complicated by sepsis with organ failure, included coagulopathy. The day after admission, the patient complained of foggy vision, and ophthalmological examination suggested bacterial endophthalmitis associated with sepsis. In the blood culture at the time of admission, a long-chain

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**Table 1. Laboratory data on admission**

| Hematology                  | Chemistry/serology                  |
|-----------------------------|-------------------------------------|
| White blood cell count      | Glucose                             |
| Red blood cell count        | Total protein                       |
| Hemoglobin level            | Albumin                             |
| Hematocrit                  | Total bilirubin                     |
| Platelet count              | Aspartate aminotransferase          |
| Arterial blood gas (room air)| Alkaline phosphatase                |
| pH                          | Lactate dehydrogenase               |
| PCO₂                        | Amylase                             |
| PO₂                         | Creatine phosphokinase              |
| HCO₃                        | Blood urea nitrogen                 |
| Base excess                 | Creatinine                          |
| Oxygen saturation           | Na                                  |
| Prothrombin time (PT-INR)   | Cl                                  |
| D-dimer                     | C-reactive protein                  |

**Fig. 1.** Abdominal plain computed tomography findings on admission show a hypodense mass in the right lobe of the liver (S7), approximately 70 × 40 mm in diameter (left), and soft tissue mass in the cecum (right).
A *Streptococcus*-like bacterium was found, which was later confirmed to be *S. intermedius* on the sixth hospital day. After the initial antimicrobial treatment with supporting therapy, which decreased the inflammatory response of the markers of blood and improved clinical conditions, such as abdominal pain or high-grade fever. Contrast-enhanced computed tomography scan of the abdomen performed on the eighth day revealed a liver abscess that presented as an approximately 7-cm-large multifocal cystic mass and intussusception of the ileocecal region with a polypoid mass in the cecum (Fig. 2). Endoscopic examination was performed to investigate the mass on the 20th day. The tumor of the cecum, the lead point of the intussusception, was demonstrated by colonoscopy, and carcinoma was diagnosed in the biopsy specimen from the tumor (Fig. 3). On the 26th day, right hemicolectomy was performed via midline laparotomy and tumor of the cecum was removed (online suppl. Fig. 2). Histologically, there was moderately differentiated ductal adenocarcinoma with vascular invasion. Metastasis was found in one affiliated lymph node among 10 affiliated lymph nodes sampled. The patient recovered and was discharged from the hospital on the 45th day of the disease. On the 98th day, the patient underwent ophthalmic surgery to repair the retina and vitreous. The patient is currently attending the outpatient clinic 4 years after the surgery with no signs of recurrence or metastasis of the carcinoma of the cecum. No liver abscesses have been observed.

**Fig. 2.** Enhanced abdominal computed tomography on the eighth day shows multiple coalescing cystic lesions of 7 cm size in the right lobe (S7) (left). Soft tissue density mass was suspected in the cecum. In this area, intussusception was suspected (right).

**Fig. 3.** Colonoscopic findings on 26th day show the tumor, which is the lead point of intussusception of the colon. This tumor was diagnosed as adenocarcinoma histologically.
Discussion/Conclusion

In the clinical setting of *S. intermedius* infection, it should be noted that the bacteria are not easy to culture and cannot be identified using routine laboratory methods. This is because this type of bacteria needs strict anaerobic conditions. Because it is also capnophilic, *S. intermedius* can grow in the presence of 5% carbon dioxide. Additionally, it is strictly auxotrophic. Even under ideal culture conditions, it is still slow growing. The colonies are pinpoint and are as small as 0.5 mm at 24 h [2].

In contrast to *E. coli* or *K. pneumoniae*, the antimicrobial susceptibilities of *S. intermedius* have not been confirmed [3]. If *S. intermedius* is suspected to be the causative organism of a liver abscess, early administration of carbapenems is recommended, although reports have been extremely limited [4]. In our case, meropenem was used as the carbapenem. We also used metronidazole as a strategy for empiric therapy, considering the possibility of ameba infection of the liver until the fourth hospital day.

The difficulty in identifying these bacteria has resulted in a historical shift in the nomination of these bacteria. It has been confirmed that *S. intermedius* are members of the *Streptococcus milleri* group or *Streptococcus anginosus* group along with *Streptococcus constellatus* and *S. anginosus* [5]. Although these bacteria are lumped together, their infectious characteristics and features have been recognized to differ among one another [6]. Among these bacteria, *S. intermedius* is a particularly important kind of bacteria because it secretes unique cytotoxins specific to human cells [7]. This fact might be related to the characteristics of the bacteria that tend to cause pyogenic abscesses in various organs, not only in the liver.

The comorbidity of cecal carcinoma in this case deserves special attention, considering the infectious source and abscess formation in the liver. Some bacteria have been implicated as risk factors for colorectal carcinoma. Examination of colorectal neoplasms is recommended for patients with bacteremia due to *S. bovis* [1], *S. sanguinis* [8], and *Clostridium septicum* [9]. The case reports concerning with the evidence were published in the 1990s. From 2000 to our knowledge, the reports of liver abscess associated with colon carcinoma by *Streptococcus* other than *S. bovis* group were rather limited to the *S. milleri* group [10–13] (Table 2).

It might also be important that *Streptococcus* genes are one of the genes of upregulated in patients with colorectal carcinoma. Recent research investigating 16S rRNA of the mucosal colon microbiome showed that genes of *S. intermedius* and other certain kinds of bacteria were significantly upregulated in patients with colorectal carcinoma compared to healthy volunteers. This extent is particularly marked for *S. intermedius* [14]. This evidence suggests that the generation of toxic metabolites from *S. intermedius* can promote an environment that favors the development of carcinoma. As for *S. bovis*, promotion of intestinal carcinogenesis was suggested, showing that the bacterial walls are potent inducers of neoplastic transformation. Although we cannot prove the direct link between this phenomenon and liver abscesses with colon carcinoma, research on *S. milleri* group including *S. intermedius* might be more promoted. In the report of Millichap et al. [12], the tumor was a 1-cm sessile polyyp in the sigmoid colon. In our case, the tumor was in the cecum. Although the sites of the tumors were different between the 2 cases, it is important that the clinical symptoms from carcinoma were not present in both cases. This fact might encourage clinicians to search colorectal neoplasm in the case of liver abscess in asymptomatic stage of tumor. In the future, we might have the evidence, which suggests the need for clinicians to take care of potential colonic diseases in cases of liver abscess with *S. milleri* including *S. intermedius*.

*S. intermedius* tends to form abscesses in various organs. The development of bacterial endophthalmitis in our case may be consistent with the characteristics of bacteria [15].

In conclusion, we report a case of pyogenic liver abscess with *S. intermedius* bacteremia. This case was accompanied by intussusception of colon of which cecum carcinoma was the
Table 2. Report cases of *Streptococcus* bacteremia associated with colon cancer other than *Streptococcus bovis* group (2000–present time)

| Authors         | Year | Age/sex     | Causative agent | Streptococcus group | Specimen of bacteria | Course of infection | Information of carcinoma (site and histological type) |
|-----------------|------|-------------|-----------------|----------------------|----------------------|--------------------|--------------------------------------------------------|
| Rawla et al. [10] | 2017 | 62 years/male | *S. anginosus*  | Milleri              | Blood                | Recovery           | Splenic flexure adenocarcinoma                        |
| Masood et al. [11] | 2016 | 62 years/male | *S. anginosus*  | Milleri              | Blood                | Recovery           | Rectus adenocarcinoma                                  |
| Millichap et al. [12] | 2005 | 55 years/male | *S. intermedius* | Milleri              | Blood aspirated fluid | Recovery           | Splenic flexure adenocarcinoma                        |
| Tzur et al. [13] | 2003 | 64 years/male | Not determined  | Milleri              | Blood aspirated fluid | Recovery           | Proximal ascending colon adenocarcinoma                |
pathological leading point. Association of pyogenic liver abscess caused by *Streptococcus* with colon carcinoma would be investigated further concerning with not only *S. bovis* but also *S. milleri* including *S. intermedius*.

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**Statement of Ethics**

All the procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study protocol was reviewed and the need for approval was waived by the Bioethics Committee of Nagayama Hospital. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**Conflict of Interest Statement**

The authors have no competing interests directly related to the content of this article.

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**Author Contributions**

Ikuo Ota, Hitoshi Takahashi, and Megumi Ono were involved in the patient’s treatment mainly supportive therapy in acute stage. Seiki Yamamoto, Akihiro Kogita, Hiroshi Tsuda, and Sadao Funai were involved in the surgical treatment. Hironori Shigeoka and Atsushi Hiraide were instrumental in the composition of the text. Ikuo Ota, Hitoshi Takahashi, Mugumi Ono, Seiki Yamamoto, Akihiro Kogita, Hiroshi Tsuda, Sadao Funai, Hironori Shigeoka, and Atsushi Hiraide read and approved the final manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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