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CASE REPORT

# Empyema Caused by Mixed Infection with *Streptococcus intermedius* and *Streptococcus constellatus* in a Patient with Previous Surgery for Oral Carcinoma: A Case Report

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**Background:** The incidence of community-acquired empyema caused by the *Streptococcus anginosus* group (SAG) has been on the rise in the 2020s. To the best of our knowledge, while empyema caused individually by either strain has been reported, there are no reports on empyema caused by concurrent infection with these two strains. Here, we report for the first time empyema caused by concurrent infection with *Streptococcus intermedius* and *Streptococcus constellatus* (both SAG species) in a postoperative patient who had been treated for floor of the mouth carcinoma.

**Case Presentation:** A 61-year-old male patient who had undergone surgical treatment for floor of the mouth carcinoma 2 year earlier suddenly presented with left-sided chest pain. Chest computed tomography (CT) revealed encapsulated pleural effusion on the left side, which was diagnosed as empyema. Metagenomic next-generation sequencing(mNGS) of the pleural fluid sample indicated mixed infection caused by *Streptococcus intermedius* and *Streptococcus constellatus*. The patient's condition improved about 5 weeks after treatment with thoracic fluid drainage and cephalosporin antibiotics.

**Conclusion:** This case highlights the possibility of concurrent infection with two SAG strains in patients with empyema. Currently, it is unclear whether there is a definitive relationship between a surgical history of carcinoma of the floor of the mouth and empyema caused by infection with SAG strains. This case could, perhaps, serve as a reference for future related research on the topic.

**Keywords:** *Streptococcus intermedius*, *Streptococcus constellatus*, oral carcinoma, pleural effusion, carcinoma of the floor of the mouth, empyema

## Introduction

Empyema is a purulent infectious process characterized by the accumulation of purulent exudate in the pleural cavity due to bacterial invasion of the pleural space.[1,2] In the United States, approximately 32,000 patients develop empyema each year, and it is associated with increased mortality rates, with about 20% to 30% of cases resulting in death of the patient or requiring further surgical intervention within the first year of empyema development.[3] Research from the 1990s indicated that community-acquired empyema was commonly caused by infections with *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae*,[4] whereas studies from the 2020s suggest a rising

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incidence of empyema resulting from infections with microbes from the *Streptococcus anginosus group* (SAG). In fact, SAG bacterial species have been surpassing *Staphylococcus aureus*,[5] and even *Streptococcus pneumoniae*, to become the primary microbial agent responsible for infections causing empyema.[6] Apart from SAG, members of the oral or nasopharyngeal microbiota, such as aggregatibacter actinomycetemcomitans and capnocytophaga, have also been reported to cause opportunistic systemic infections, including empyema.[7–9] *Streptococcus intermedius* and *Streptococcus constellatus* are typical SAG species present in the oral, upper respiratory, and gastrointestinal microbiota and are commonly associated with dental plaque and periodontal disease, although they can also invade the circulation and lead to the development of empyema.[10,11]

Empyema can be caused by more than one microorganism, with approximately 14% of cases involving polymicrobial infections commonly including anaerobic bacteria.[5,12,13] Compared to single infections, mixed infections often indicate poorer prognosis for patients, irrespective of whether they involve aerobic or anaerobic bacteria.[12,14] SAG species also often form mixed infections with other bacteria, especially anaerobic bacteria. Multiple studies suggest that among patients with respiratory infections caused by SAG, 30%–83% have monomicrobial infections, while 13%–45% have concurrent infections caused by other bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa*, and anaerobic bacteria, with a co-infection rate of 14%–24%.[15–17] Studies have found that the one-year mortality rate for empyema caused solely by streptococci or anaerobic bacteria is approximately 20%, with no significant difference between them. Empyema caused by mixed infections has a mortality rate of around 45%.[14] However, the data are currently based on statistics from a small number of cases and lack validation from studies on large patient samples. Additionally, there are currently no reported cases of empyema caused by mixed infections with two SAG strains. Here, we hope to contribute to the literature by presenting a case of a postoperative patient with carcinoma of the floor of the mouth who had undergone surgical treatment 2 years earlier and developed empyema caused by a mixed infection with *Streptococcus intermedius* and *Streptococcus constellatus*, which was successfully treated with a combination of thoracic fluid drainage and an antibacterial regimen.

## Case Presentation

The patient was a 61-year-old male farmer of Han ethnicity. The patient had a 20-year history of smoking but denied having a history of alcohol consumption. On May 7, 2021, during a routine physical examination, ultrasound imaging revealed a mass on the medial edge of the patient's left submandibular gland. The patient underwent surgical treatment at our hospital on May 31, 2021. Postoperative pathological analysis revealed a low-grade mucinous epidermoid carcinoma of the left side (size: 2.1×1.1 cm), without evidence of metastasis. He was followed up at the outpatient department at the 4-month and 17-month marks, with no tumor recurrence detected. (Figure 1). During the postoperative follow-up period, the patient did not perform any special oral care other than brushing and rinsing his mouth before breakfast each day.

Unfortunately, he presented to our hospital on December 18, 2023, with left-sided chest pain that he had been experiencing for one week without any apparent cause. Physical examination indicated that the patient developed a fever, with a maximum temperature of 38.9°C, a heart rate of 93 beats per minute, and a blood pressure of 131/84 mmHg. Lung auscultation revealed diminished breath sounds in the left lung, with no significant crackles or rhonchi heard. Cardiac auscultation did not yield any remarkable findings, and no pitting edema was observed in the face, limbs, or lower extremities upon palpation. Laboratory tests indicated a white blood cell (WBC) count of $11.9\times10^9$ cells/L (normal range: 3.5–9.5 × $10^9$ cells/L); neutrophil count, $10.70\times10^9$ cells/L (normal range: 1.8–6.3 × $10^9$ cells/L); C-reactive protein (CRP) level, 168.7 mg/L (normal range: 0–6 mg/L); procalcitonin (PCT), 0.42 ng/mL (normal level: <0.05 ng/mL); albumin, 35.9 g/L (normal range: 40–55 g/L); glucose, 6.9 mmol/L (normal range: 4.3–5.9 mmol/L); D-dimer, 3.89 μg/mL (normal range: 0–0.5 μg/mL); cancer antigen 125 (CA125), 88.69 U/mL (normal level: <35 U/mL); and ferritin, 958.5 μg/L (normal range: 30–400 μg/L) (Table 1). Liver enzymes, creatinine, and electrolytes were within normal limits, and the patient tested negative for human immunodeficiency virus(HIV), syphilis, and hepatitis B. Chest CT scan showed bronchiectasis at multiple sites with surrounding inflammation in the upper and lower lobes of the right lung, a small area of pleural effusion with adjacent lung tissue atelectasis in the left chest, and a small area of encapsulated effusion in the left oblique fissure (Figure 2A–C). Under aseptic conditions, ultrasound-guided thoracentesis was performed on the left side on December 22, 2023. Analysis of the drained fluid revealed bloody pleural fluid. Further,

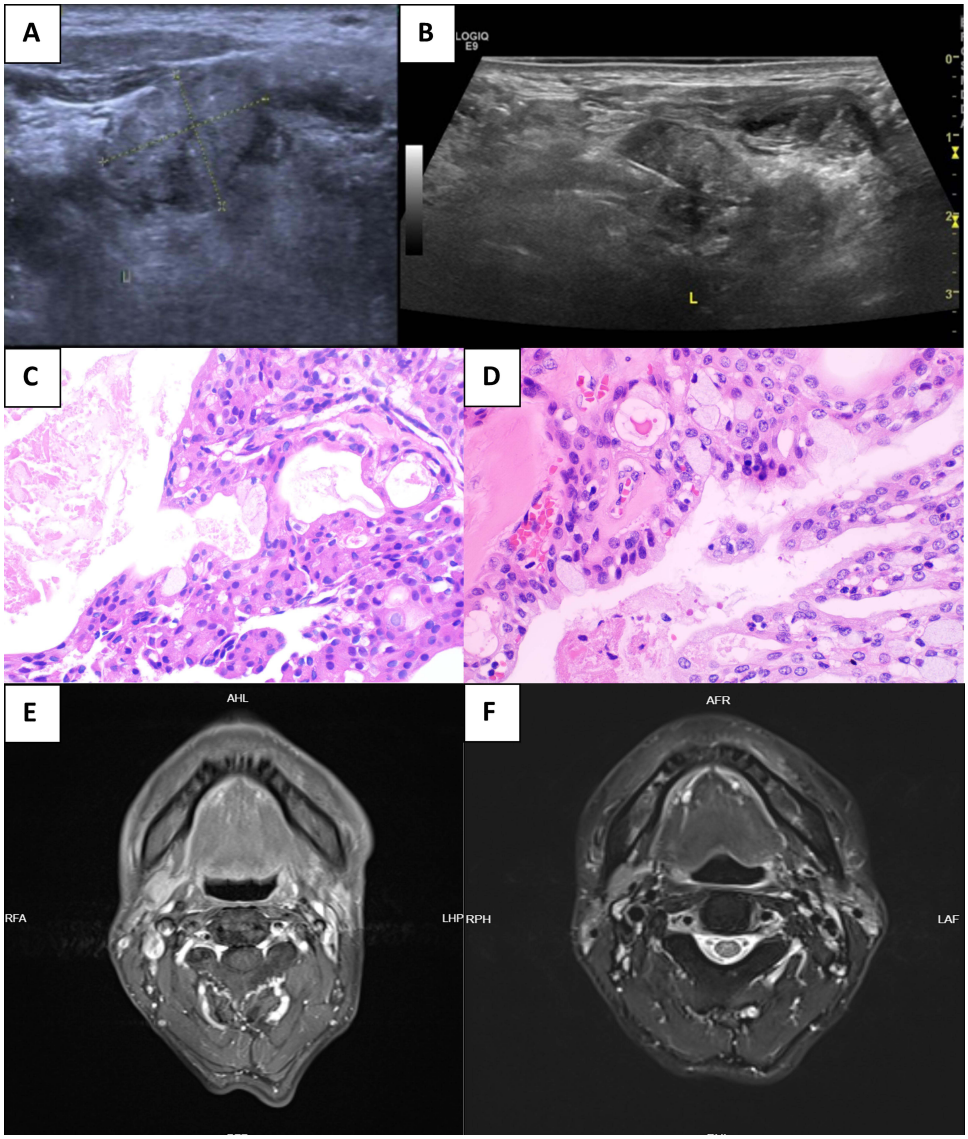


**Figure 1** Previous imaging and histopathological observations related to the diagnosis and surgical treatment of oral mucinous carcinoma. (**A**) On May 7, 2021, ultrasound imaging revealed a moderately echogenic mass approximately 2.17×1.47 cm in size on the deep medial edge of the left submandibular gland. (**B**) On May 18, 2021, an ultrasound-guided needle biopsy of the mass was performed. (**C**) Pathological image of a needle biopsy sample obtained on May 25, 2021, showing a salivary gland tumor, based on which mucoepidermoid carcinoma could not be excluded. (**D**) On May 31, 2021, the patient underwent sublingual gland lesion excision, sublingual gland resection, functional neck lymph node dissection, and salivary gland resection. Postoperative pathological image obtained on June 7, 2021, indicated a low-grade mucoepidermoid carcinoma (size 2.1×1.1 cm) in the left sublingual gland and left submandibular gland salivary tissue, and one lymph node in the left neck at levels 1 and 2, with no cancer metastasis. (**E** and **F**) E and F represent the oropharyngeal MRI followed up on October 8, 2021 and November 24, 2022, respectively; Both indicate that the patient has no oral carcinoma recurrence.

the WBC count of the pleural fluid was 132 cells/μL; neutrophil percentage, 60%; lymphocyte percentage, 35%; lactate dehydrogenase, 572 IU/L; Rivalta test, weakly positive; and total protein, 47 g/L (Table 2). No malignant tumor cells were detected on cytological examination of pleural fluid, and the pleural fluid culture was not positive for any bacterial or fungal species. However, metagenomic next-generation sequencing of pleural fluid indicated infection with *Streptococcus intermedius* and *Streptococcus constellatus*.

On admission, empirical treatment with intravenous ceftriaxone (dosage 1 g, q8h) was started. Based on the mNGS results, antibiotic therapy was adjusted to intravenous ceftriaxone at 2 g qd. The patient's temperature gradually normalized, and chest pain was also alleviated. The patient was discharged on December 29, 2023, and treatment with oral cefixime capsules (0.1 g bid) was continued for 4 weeks. On January 25, 2024, that is, 45 days after the start of antibiotic treatment, the patient reported no significant discomfort. Follow-up chest CT scan at our hospital showed

**Table 1** Results of the Hematological Tests Conducted During Hospitalization

| Laboratory Test | Result |
|---|---|
| White Blood Cell Count (3.5–9.5 × $10^9$ cells/L) | 11.9 |
| Neutrophil Count (1.8–6.3 × $10^9$ cells/L) | 10.7 |
| Hemoglobin Concentration (130–175 g/L) | 109.0 |
| Platelet Count (125–350 × $10^9$ cells/L) | 351.0 |
| C-Reactive Protein Concentration (<6.0 mg/L) | 168.7 |
| Procalcitonin (<0.05 ng/mL) | 0.4 |
| Alanine Aminotransferase (9–50 U/L) | 26.0 |
| Aspartate Aminotransferase (15–40 U/L) | 24.0 |
| Albumin (40.0–55.0 g/L) | 35.9 |
| Serum Creatinine (57–111 μmol/L) | 74.0 |
| Random Postprandial Blood Glucose (3.9–11.1 mmol/L) | 6.9 |
| Glycated Hemoglobin A1c (4.00–6.00%) | 5.7 |
| Troponin I (0–54 ng/L) | <2.5 |
| N-terminal pro b-type Natriuretic Peptide (<900 pg/mL) | 254.0 |
| Cancer Antigen 125 (<35.00 U/mL) | 88.7 |
| Ferritin (30.00–400.00 μg/L) | 958.5 |
| D dimer (0.00–0.50 μg/mL) | 3.9 |
| QuantiFERON-TB Gold Test (QB-SPOT) | Negative |

significant absorption of the left pleural effusion compared to previous images, with residual patchy shadows in the left lower lobe (Figure 2D–F). Follow-up was continued, and on March 19, 2024, a repeat chest CT scan was performed. The image showed further resolution of the patchy shadows in the left lower lobe compared to the previous follow-up image (Figure 2G–I).

## Discussion

In this report, we have described a case of mixed infection with the SAG species *Streptococcus constellatus* and *Streptococcus intermedius* that led to empyema in a patient who had previously undergone surgery for cancer of the foot of the mouth. The observations made in this case and their implications are discussed below, along with supporting literature.

The genus Streptococcus is composed of over 130 species of gram-positive, catalase-negative bacteria.[18] The SAG is included among them. SAG species can cause intrathoracic infections through inhalation of oral secretions, direct invasion via trauma or surgery, extension of adjacent tissue infections, and hematogenous spread.[19] Respiratory infections caused by SAG species can easily lead to pleural effusion, and even empyema. For example, Okada et al conducted a retrospective study on 33 patients with SAG pulmonary infections and found that 18 cases (54.5%) had pleural effusion, including 7 cases (21.2%) with bilateral effusion, 11 cases (33.3%) with unilateral effusion, and 7 cases (21.2%) with complex effusion.[20] Further, analysis of pleural effusion in 5 patients with recurrent effusion revealed the presence of empyema in all cases.[20] In another analysis of 30 patients with SAG respiratory tract infections, it was found that 22 patients (73.3%) had pleural effusion, with half of them developing empyema.[10] Among the patients with pleural effusion, 16 (53.3%) were infected with *Streptococcus intermedius*, and 11 (36.7%), with *Streptococcus constellatus*.[10]

Some of the reported risk factors for empyema caused by *Streptococcus constellatus* include advanced age, diabetes, oral infections, and oral surgery.[17] It is known that patients with underlying diseases, especially cancer, are more susceptible to SAG infections. For instance, Jiang et al analyzed 463 cases of SAG infections, of which 210 (45.4%) had underlying diseases, including 63 cases of solid tumors (30%) and 6 cases of hematologic malignancies (2.86%).[21] Additionally, oral malignant tumors, as a type of solid tumor, have been further been confirmed to be a factor that predisposes patients to SAG infections. Sasaki et al found that among 49 patients with oral malignant tumors, 19 were diagnosed with SAG infections,[22] and another study on oral squamous cell carcinoma also found high expression of

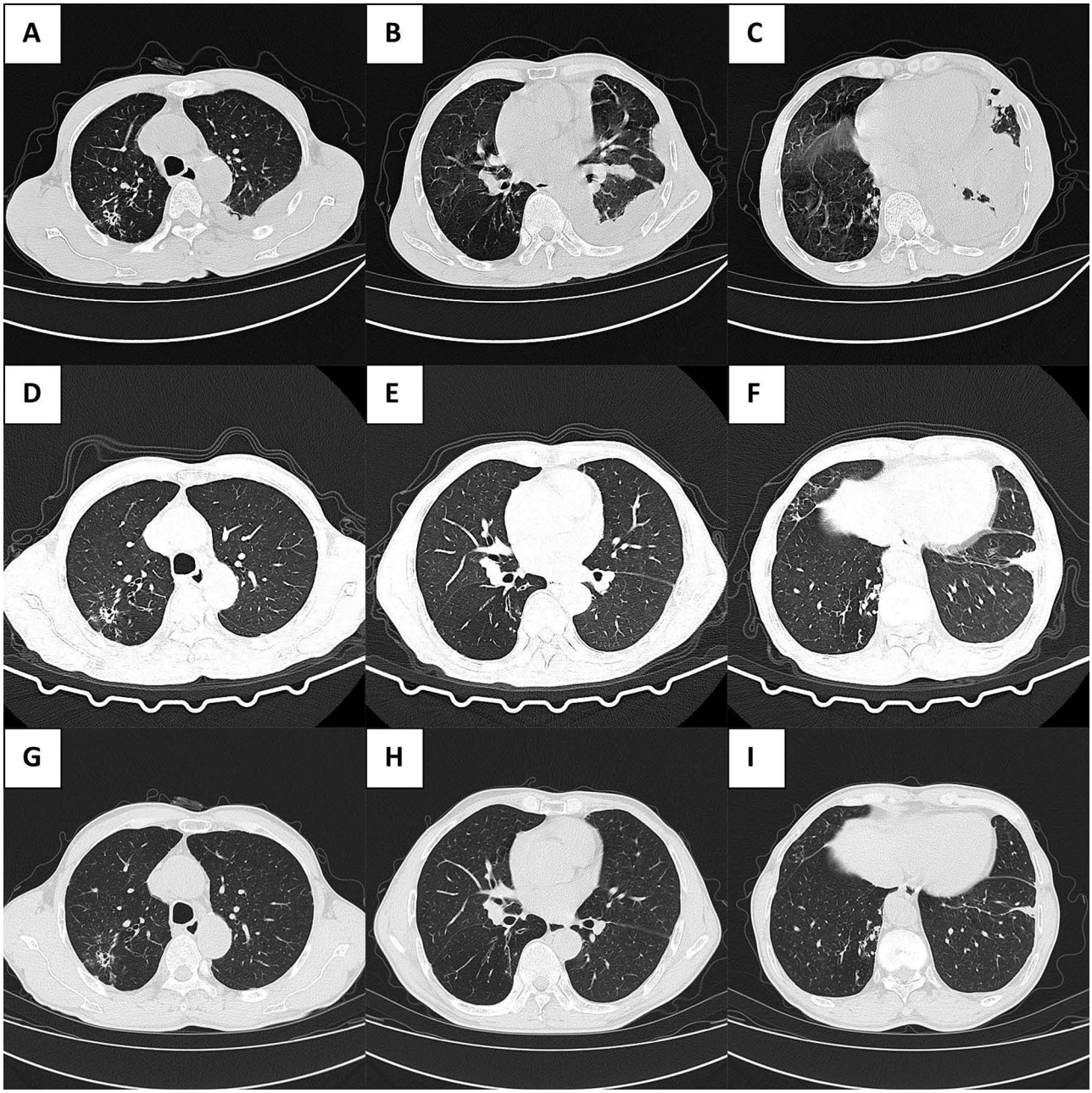


**Figure 2** Pre-treatment and follow-up computerized tomography (CT) images. (**A**–**C**) Pre-treatment CT scan showing a small amount of pleural effusion in the left thoracic cavity with adjacent lung tissue atelectasis and a small amount of encapsulated effusion in the left oblique fissure. (**D**–**F**) Follow-up CT scan obtained after approximately 5 weeks of anti-infection treatment showing significant absorption of the pleural effusion in the left thoracic cavity compared to previous scans. (**G**–**I**) Further follow-up observation at 7 weeks showing continued absorption of the left lower lobe streaky shadow compared to previous scans.

*Streptococcus constellatus*.[23] Streptococcus anginosus is also a member of the SAG. Mäkinen et al collected saliva samples from 99 patients with oral squamous cell carcinoma at the beginning of their treatment path and found that the relative abundance of *Streptococcus anginosus* was higher in the saliva of the oral cancer patients compared to healthy individuals.[24] They further conducted a follow-up study with a mean follow-up time of 48 months on 28 postoperative oral squamous cell carcinoma patients and discovered that the abundance of *Streptococcus anginosus* in the patients' saliva had decreased.[24] Although our patient was infected with *Streptococcus intermedius* and *Streptococcus constellatus*, which are different from *Streptococcus anginosus*, all of them belong to the SAG. Therefore, we speculate that the abundance of SAG in oral cancer patients might change over the follow-up period. However, there are some limitations

**Table 2** Result of Pleural Fluid Analysis

| Pleural fluid parameters | Result |
|---|---|
| Red Blood Cell Count (cells/μL) | 41000 |
| White Blood Cell Count (0–100 cells/μL) | 132 |
| Neutrophil Percentage | 60% |
| Lymphocyte Percentage | 35% |
| Mesothelial Cell Percentage | 4% |
| Macrophage Percentage | 1% |
| Rivalta test | Weak positive |
| pH | 8 |
| Total Protein Content (g/L) | 47 |
| Albumin Level (g/L) | 27 |
| Lactate Dehydrogenase Level (60–213IU/L) | 572 |
| Adenosine Dehydrogenase Level (IU/L) | 14 |
| Glucose Level (mmol/L) | 5.3 |
| Carcinoembryonic Antigen Level (ng/mL) | 1.3 |

in their study: Firstly, given the relatively small sample size, further studies are required to validate the reliability of these results. Secondly, after the follow-up observations, they only compared the results with the preoperative data and did not compare them with a healthy control group. Therefore, it remains unclear whether the abundance of Streptococcus anginosus in the oral cavity is still higher than that in the healthy control group after the follow-up period. Thirdly, although the abundance of *Streptococcus anginosus* decreased after follow-up, it is not clear whether this reduction is of clinical significance. Therefore, we consider that whether a surgical history of oral cancer, especially in patients with long-term follow-ups with no recurrence, poses a high risk of SAG infections leading to empyema remains to be further researched.

SAG species can produce high concentrations of the carcinogenic metabolite acetaldehyde from alcohol.[25] In patients with oral cancer, acetaldehyde may induce the production of inflammatory cytokines, such as interleukin-1-beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), and thereby lead to chronic inflammation.[26] Thus, the mechanism of SAG infections in patients with cancer may involve increasing degrees of inflammation. However, the risk of SAG infection after surgery for tumors is unclear and requires further investigation. Furthermore, the current research on SAG infections in oral malignant tumors primarily focuses on oral squamous cell carcinoma, while the relationship between oral mucinous carcinoma and SAG infection remains inconclusive and requires further study.

Thoracic drainage and antibiotic therapy are effective treatments for empyema. Jacobs et al collected 423 strains of SAG and conducted susceptibility tests for 12 antibiotics.[27] The results showed that only 1.4% of the strains were moderately sensitive to penicillin, and none of the strains were highly resistant to gentamicin.[27] Further, the resistance rates to erythromycin, roxithromycin, and clindamycin were 2.6%, 2.4%, and 2.4%, respectively, with 5.7% of the strains showing resistance to doxycycline.[27] Moreover, all the strains were sensitive to ceftriaxone, vancomycin, and teicoplanin.[27] Rams et al found that in vitro isolated strains of *Streptococcus constellatus* and *Streptococcus intermedius* were almost completely sensitive to amoxicillin, clindamycin, and azithromycin, moderately sensitive to ciprofloxacin, and almost resistant to metronidazole.[28] In addition, Lin et al found that *Streptococcus constellatus* strains isolated from 9 empyema patients were completely sensitive to penicillin, linezolid, levofloxacin, and vancomycin, and exhibited a sensitivity rate of 87.5% to ceftriaxone; however, the strains exhibited a very low sensitivity rate of 37.5% to tetracycline and clindamycin.[17] The recommended antibiotic course for empyema is generally 2 to 6 weeks (initially intravenous and then oral) of treatment, depending on the severity of infection and the patient's clinical response to treatment.[29] In the present case, the patient underwent thoracic puncture drainage and received cephalosporin antibiotics. With this strategy, the infection was effectively inhibited for approximately 5 weeks, and the patient showed good recovery.

This report also some limitations that need to be considered when interpreting the findings. First, we did not perform microbiological testing of the patient's oral microbiota before and after surgery or during empyema to further assess the patient's oral microbiota and verify whether the SAG species causing empyema match those present in the oral cavity. As the oral microbiome is closely associated with aspiration pneumonia,[30] it would be interesting to explore this possibility. Second, there was no control group, given that this is a single case report. Therefore, it was not possible to discuss differences in the prognosis of empyema caused by single *Streptococcus intermedius* or *Streptococcus constellatus* infection and empyema caused by mixed infections. Third, while the most recent follow-up chest CT showed that most of the left lower lobe empyema had been absorbed, some residual patchy shadows that had not completely resolved were still present. This indicates the need for further follow-up and vigilance for possible recurrence of empyema.

Despite the limitations mentioned above, this case report is significant as it is an uncommon one that documents a patient who developed empyema caused by both *Streptococcus intermedius* and *Streptococcus constellatus* after surgery for oral mucinous carcinoma. The findings also underscore successful treatment outcomes with strategies that are typically used in cases of empyema caused by SAG species. We believe that this report provides valuable insights for future clinical diagnosis and treatment of mixed SAG infections and related research.

## Data Sharing Statement

This article provides a detailed account of the original data for this case report, which can be shared without requiring institutional approval. For additional information, please contact the corresponding authors.

## Ethics Approval and Informed Consent

This study was reviewed and approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, China. Written informed consent has been provided by the patient to have the case details and any accompanying images published.

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## Disclosure

The authors have no conflicts of interest to declare.

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