Pyogenic spinal infections in patients with chronic liver disease: illustrative case and systematic review

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BACKGROUND Pyogenic spinal infections (PSIs) are a group of uncommon but serious infectious diseases that are characterized by inflammation of the endplate-disc unit. PSIs are considered more prevalent and aggressive among patients with chronic immunocompromised states. Association between PSIs and liver disease has not been systematically analyzed. The authors performed a systematic review to study baseline characteristics, clinical presentation, and mortality of patients with PSI in the setting of chronic liver disease.

OBSERVATIONS The authors presented the case of a 72-year-old female patient with chronic liver disease who presented with severe low back pain and bilateral lower weakness. Imaging studies showed T10–11 spondylodiscitis. The patient received decompression and fusion surgery with partial neurological improvement. The authors performed a systematic literature search of spondylodiscitis and liver disease, and eight published articles met the studies inclusion and exclusion criteria. These studies featured a total of 144 patients, of whom 129 met inclusion criteria (mean age, 60.5 years, range 40 to 83 years; 62% males). Lumbar infection was the most common report (67%), with Staphylococcus aureus (48%) as the main causative microorganism. Neurological compromise was present in 69% of patients. Surgical intervention occurred in 70.5% of patients, and the average duration of antibiotic treatment was 69.4 days. Postoperative complication rate was 28.5%, with a 30- and 90-day mortality of 17.2% and 24.8%, respectively.

LESSONS Pyogenic spondylodiscitis in patients with liver disease was associated with a high rate of neurological compromise, postoperative complications, and mortality.

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KEYWORDS vertebral osteomyelitis; spondylodiscitis; liver disease; cirrhosis; pyogenic spinal infection

Pyogenic spinal infections (PSIs) are a group of uncommon but serious infectious diseases that are characterized by inflammation of the disc–vertebral unit. With an estimated prevalence of 5.4 per 100,000 in Western societies,1 PSIs encompass a range of clinical conditions, including spondylitis, discitis, spondylodiscitis, vertebral osteomyelitis (VO), epidural abscess, and paravertebral abscess. These conditions have been shown to be more prevalent among patients above 65 years with chronic debilitating conditions (uncontrolled diabetes mellitus and immunocompromised states), intravenous drug users, and persons with alcoholism, sickle cell anemia, HIV infection, malignancy, renal failure, liver cirrhosis, rheumatologic diseases, and history of previous spinal surgery.1 Despite the historical scarcity of PSI, its incidence appears to be on the rise. This observation is likely secondary to the increasing prevalence of immunocompromised persons, increasing numbers of invasive spinal procedures, intravenous drug abuse, increasing life expectancy for patients with chronic debilitating diseases, emergence of drug-resistant microorganisms, and development of complex comorbidities. Additionally, it is likely that higher diagnostic awareness and yield have played a role in the increased incidence of PSI.3–6 This is important because PSI has historically been diagnosed late in the disease course as a result of its association with nonspecific symptoms such as generalized back pain. This clinical characteristic paves the way for infectious spread with neurological complications and even death.7

ABBREVIATIONS CRP = C-reactive protein; PSI = pyogenic spinal infection; VO = vertebral osteomyelitis.

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Diagnosing PSIs is a multidisciplinary effort requiring input from radiology, spine surgery, nuclear medicine, and infectious disease specialists. When paired with the nonspecificity of symptoms, what begins as low-grade inflammation can progress into debilitating infection if not diagnosed and treated within a reasonable time frame. This is especially true in immunocompromised patients with comorbidities such as end-stage renal disease and liver disease and patients receiving organ transplants. For example, patients with chronic liver disease may have increased morbidity and mortality due to variceal bleeding, ascites, and hepatic carcinoma, each of which can complicate a diagnosis of PSI.8,9,10 Regarding the association between PSI and chronic liver disease, some studies have suggested a higher rate of neurological compromise, epidural abscess, and mortality in this group of patients.11,12

We report an illustrative case of an aggressive pyogenic spondylodiscitis in a patient with chronic liver disease. To our knowledge, no systematic review concerning the overall incidence, characteristics, prognosis, and estimated mortality in patients with PSI secondary to liver disease has been performed. Therefore, the objective of this study is to analyze, through a systematic literature review, the baseline characteristics, clinical presentation, and mortality of patients with PSI in the setting of chronic liver disease.

Illustrative Case

A 72-year-old woman presented to the outpatient clinic with severe low back pain that had started approximately 25 days earlier. She reported no traumas or falls, and she had referred progressive bilateral leg weakness over the last 7 days.

On physical examination, tenderness to palpation was confirmed at the thoracolumbar region. Bilateral lower extremity strength was 3/5 for quadriceps and soleus muscles groups and 5/5 for the other muscle groups. Patellar reflexes were 3+ bilaterally, and positive clonus was detected.

Imaging studies revealed an aggressive spondylodiscitis at T10–11 levels (Fig. 1). Patient past medical history revealed chronic liver disease due to nonalcoholic steatohepatitis and smoking as positive background.

Preoperative C-reactive protein (CRP) and sedimentation rate were 102 and 95 mg/L, respectively, white blood cell count was 13,500, and blood culture was positive for Staphylococcus aureus.

Surgery was performed through posterior approach, a T9–L1 posterior instrumentation with T10–11 laminectomy, and interbody debridement mesh cell (Fig. 2). The operative time was 180 minutes, with estimated blood loss of 400 mL. The patient experienced partial improvement of motor strength and was able to ambulate with use of a walker. She completed an 8-week course of antibiotics and showed improvement of laboratory parameters.

Discussion

Observations

Primary spinal infections in patients with chronic liver disease may behave differently in terms of epidemiology, clinical presentation, and outcomes compared with patients without liver disease. A systematic literature search was performed in PubMed, Web of Science, and Google Scholar in November 2021 to identify studies reporting the outcome of pyogenic spinal infection in patients with either liver cirrhosis or chronic liver failure. The search strategy was developed by one author (G.C.W.) by consulting the Peer Review of Electronic Search Strategies (PRESS) criteria.13 The search strategy for PubMed, Web of Science, and Google Scholar is displayed in Table 1. We performed the literature search with records filtered from January 2000 to November 2021. We included retrospective case series and individual case reports. Study selection was performed by three authors (N.B., R.B., and M.H.), and data extraction was performed by one author (N.B.). Full articles were retrieved when authors found titles and abstracts potentially relevant.
The sample size across all studies was 144 patients, with 129 remaining after application of inclusion and exclusion criteria. This cohort of 129 patients ranged in age from 40 to 83 years. The mean age was 60.5 years. There were 80 men (62%) and 49 women (38%). Etiologies for liver disease were reported for all 129 patients and included alcohol (n = 54; 41.9%), virus (n = 53; 41.1%), nonalcoholic steatohepatitis (n = 9; 6.9%), cystic liver disease (n = 2; 1.5%), liver cancer (n = 1; 0.7%), and other (n = 10; 7.7%). Child-Turcotte-Pugh score was reported for 122 patients, of whom 10.6% (n = 13) had class A, 36.1% (n = 44) had class B, and 53.3% (n = 65) had class C.

Local pain and fever were reported for 44 patients, of whom 97.7% (n = 43) presented with local pain and 45.4% (n = 20) presented with fever. Neurological deficit was present in 89 patients (69%). Septic manifestation was present in 67 patients (51.9%). Individual leukocyte levels were reported for 44 patients, of whom 36.3% (n = 16) presented with elevated white blood cell count. Individual CRP levels were reported for 41 patients, of whom 100% (n = 41) presented with elevated levels. Level of spinal infection was reported for 100 patients, of whom 13% (n = 13) presented with cervical infection, 31% (n = 31) presented with thoracic infection, and 67% (n = 67) presented with lumbar infection. Epidural abscess was reported for all 129 patients, of whom 79.8% (n = 103) presented with epidural abscess. Psoas abscess was reported for 44 patients, of whom 29.5% (n = 13) presented with psoas abscess.

The main causative organism of spinal infection was reported for all 129 patients. Staphylococcus aureus was reported as the main causative organism in 48% (n = 62) of patients, of whom 40.3% (n = 25) were methicillin resistant. Gram-negative microorganisms infected 17.8% (n = 23) of patients. Other causative organisms included Enterococcus (3.1%; n = 4), other Staphylococcus species (4.7%; n = 6), Streptococcus (0.7%; n = 1), Escherichia coli (0.7%; n = 1), and Pasteurella multocida (0.7%; n = 1). In 19.4% of cases (n = 25), causative microorganisms were not specified and reported as “other.” No microorganism growth was reported in 7.7% (n = 10) of patients. Time between onset of symptoms and diagnosis was reported for 36 patients, with an average of 44.2 days. Antibiotic duration was reported for 98 patients, with an average of 69.4 days.

The type of treatment (conservative versus surgery) was reported for all 129 patients, of whom 76.7% (n = 99) underwent surgery. The combined anterior and posterior approach was performed in 77.8% (n = 28) of patients and the minimally invasive approach in 83.3% (n = 30) in Abdelrahman et al.15 These approaches were followed by posterior only 13.9% (n = 5) and anterior only in 2.8% (n = 1). Notably, Kim et al.16 made the designation of “early surgery,” defined as a surgical treatment performed under general anesthesia within 30 days after pyogenic vertebral osteomyelitis diagnosis (n = 34 patients), of whom 28.5% (n = 9) underwent spinal instrumentation. One patient from Cross and Howell17 received uneventful L4–5 laminectomy and drainage of an L4–5 abscess, and one patient from Webster et al.20 received urgent neurosurgical evacuation of a T9–12 epidural abscess. In one patient reported by Sakaguchi et al.,21 open drainage operation was performed to control infection upon diagnosis of a retropharyngeal abscess. Lastly, in Lin et al.,22 2 patients out of 14 who met our inclusion criteria received successful full endoscopic debridement and drainage. All fourteen patients reported immediate relief from pain (especially back pain) after this procedure.
Postoperative complications occurred in 30.7% (n = 28) of cases; 46.4% (n = 13) of postoperative complications involved a recurrence of infection, 28.5% (n = 8) involved a surgical site infection, and 25% (n = 7) involved surgical instrument failure. Mean follow-up time was reported for 42 patients, with an average of 677 days (range, 21–772).

One-year mortality rates were reported for all 129 patients, of whom 28.9% (n = 37) had died after 1 year; 90-day mortality rates were reported for 93 patients, of whom 24.8% (n = 32) had died after 90 days; and 30-day mortality rates were reported for 93 patients, of whom 17.2% (n = 16) had died after 30 days.

Limitations
Our study has some limitations that should be discussed. First, the articles included in our review were categorized as level IV evidence, including retrospective cases series and case reports with inherent limitations of a retrospective nature study. However, considering that both pyogenic infections and liver disease are relatively uncommon, the authors believe this is the expected evidence provided by the literature and should not be underestimated. This could also be considered a bias in the results presented in this study. On the other hand, we provided the evidence reported by the authors, and in this regard, this is the first study that systematically summarized and reported the association between spinal infections and liver disease.

Lessons
We performed a systematic review of patients with primary PSI and chronic liver disease and found that the main etiology of liver disease was alcohol-related, the most common clinical presentation was neurological deficit, 70.5% of patients required surgical treatment, with postoperative complication rates of 30.8%; and 30-day, 90-day, and 1-year mortality rate were 17.2%, 24.8%, and 28.9%, respectively.

The presence of liver disease is understood to be a risk factor for pyogenic infections for various reasons such as higher rate of bacteremia, abnormal intestinal permeability with subsequent bacterial translocation, increased number of invasive procedures, and decrease in neutrophil,

FIG. 3. PRISMA study selection flow diagram.
| Authors & Year       | Study Design | No. of Pts | Age (yrs), Sex | Etiology (n) | Segments Affected (n) | Microorganism (n) | Neurological Deficit (n) | Op (n) | Time Btw Sxs & Op (days) | Antibiotic Tx Duration (days) | Mean FU (days) |
|----------------------|--------------|------------|----------------|--------------|-----------------------|-------------------|-------------------------|--------|--------------------------|-----------------------------|-----------------|
| Abdelrahman et al., 2020 | Case series | 36         | Mean, 60.7 (range, 41–80), 26 M (72.2%), 10 F (27.8%) | Alcohol (22); nonalcoholic steatohepatitis (9); viral hepatitis (3); cystic liver disease (2) | Cervical (8); thoracic (16); lumbar (23) | Staphylococcus aureus (17); MRSA (4); S. epidermidis (5); Enterococcus (4); gram-negative (2); Streptococcus (1) | 24     | 32                      | Mean, 33.5 (± 25.1)       | 56              |
| Kim et al., 2019     | Case series  | 85         | Mean, 60.5 (± 8.7), 50 M (58.9%), 35 F | Viral (47); alcoholic (29); other (9) | Cervical (4); thoracic (13); lumbar (39) | S. aureus (42); MRSA (21); other gram-positive (15); gram-negative Enterobacteriaceae (18); other (10) | 60     | 62                      | Win 7 (9), btwn 7 & 28 (25) | Mean, 77.1 (± 28.3) |
| Malek et al., 2019   | Case report 1 | 1          | 60, M | Viral (hepatitis C) (1) | Lumbar (1) | Gram-negative Pasteurella multocida (1) | NA     | NA                      | 183 (from Sxs to Dx)       | 63              |
| Stanescu et al., 2018 | Case report | 1          | 53, F | Alcohol (1) | Lumbar (1) | Gram-negative Enterobacter spp. (1) | 1      | NA                      | 14 (from Sxs to Dx)        | 3               |
| Cross & Howell, 2003 | Case report 2 | 2          | 47, F; 54, F | Alcohol (1); viral (1) | Lumbar (2) | S. aureus (2) | 1     | 1                       | NA; 21; 122 | 84; 21          |
| Webster et al., 2007 | Case series 4 | 4          | 40, M | Viral/IVDU (1) | Thoracic (1) | S. aureus (1) | 1     | 1                       | 2                       | 56              |
| Sakaguchi et al., 2017 | Case report | 1          | 67, M | Alcohol (1) | Cervical (1) | Gram-negative Escherichia coli (1) | NA     | 1                       | 2                       | 46              |
| Lin et al., 2019     | Case series 14 | 14         | 83, M; 72, F | Liver cancer (1); other (1) | Thoracic (1); lumbar (1) | Staphylococcus (1) | 2     | 2                      | 426; 92       | 77; 49          |

Dx = diagnosis; FU = follow-up; IVDU = intravenous drug use; NA = not applicable; Op = surgery; Sxs = symptoms; Tx = treatment.
et al., reported 72% preoperative neu-

of bacteremia and, consequently, risk of infection.23,24,37,38

membrane disruption due to invasive procedures (central and urinary

and reticuloendothelial systems and higher rate of skin and mucous

the risk of epidural abscess and neurological compromise because liver

Pola et al. found a 23% rate of neurological de

surgical complications and mortality were also higher compared with

patients without liver disease. In this regard, our findings suggest that

spondylodiscitis in patients with chronic liver disease could con-
tinue to the higher mortality found in this population.

Our study showed that patients with spondylodiscitis and chronic

liver disease had higher rates of epidural abscess and neurological

compromise and, therefore, indication for surgery. Moreover, postop-

erative complications and mortality were also higher compared with

patients without liver disease. In this regard, our findings suggest that

spondylodiscitis appears to be more aggressive in this population.

This observation should be considered at the time of treating this se-

vere combination, with efforts aimed at improving patient condition

and decreasing the rate of postoperative complications and mortality.

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catheter, endotracheal intubation) can put these patients at a higher risk of bacteremia and, consequently, risk of infection.23,24,37,38

That spondylodiscitis in this population appears to be more ag-

gressive may explain higher indications for surgery; our study showed that surgery was performed in 91 patients (70.5%). Similar

results were reported by Pojskic et al.,26 the authors treated 221 of

237 patients (93%) surgically. Similar to our findings, the authors re-

ported a high rate of neurological compromise. On the other hand, in 250 patients with spondylodiscitis with 2 years of follow-up, Pola

et al.22 performed surgery in 101 (44%). The main indications for

surgery in their study were neurological compromise and segmental

instability. Our study also showed a high rate of postoperative

complications (n = 28; 30%) compared with other series such as

Pojskic et al. (21%) and Pola et al. (3.6%).

Regarding mortality, our study showed a 1-year mortality rate of

28.9%. This value is considered higher compared with the rates re-

ported in the literature by most of the studies (1.8%–24%).23,33,34,39–42

In a cohort of 298 patients with spondylodiscitis, Kehrer et al. found a 1-year mortality rate of 20%, and among factors associated with increased mortality, the authors mentioned abscess formation and neurological deficit as well as alcohol dependence and immu-
nocompromised status as predictors of mortality. Madhavan et al.,33 in a systematic review of 212 patients with spondylodiscitis and

end-stage renal disease, found a mortality rate of 24%. Both liver and renal disease are well-known factors associated with increased

mortality in patients without spondylodiscitis.44–45 In our study, we believe that the same factors that explain the higher aggressiveness of

spondylodiscitis in patients with chronic liver disease could con-

tribute to the higher mortality found in this population.

Streptococcus species frequently isolated as causative

agents of PSIs.6,27 Notably, infections with

Streptococcus and

the risk of PSI could also explain more aggressive infections. In their study con-

factors that predispose patients with chronic liver disease to higher risk

of PSI are associated with a higher rate of complications and a trend

toward higher mortality.28 VO can originate exogenously, such as direct

infection after injury to a wound and bone, or endogenously, in which

infection spreads from other areas of the body, such as in endocardi-
tis.29 Patients with liver cirrhosis have frequent bacteremias brought

about physiologically by increased intestinal permeability, immune dys-

function, and the need for frequent invasive procedures. Liver cirrhosi-
s–associated immune dysfunction involves changes to both innate and

acquired immunity via increased systemic inflammation and immuno-de-
ficiency. Persistent stimulation of immune cells leads to the production

of proinflammatory cytokines. An exaggerated inflammatory response in

cirrhosis caused by increased intestinal translocation of bacteria in-

creases the occurrence of systemic bacterial infections.30,31

Interestingly, our study showed a relatively high rate of neurolog-

ical compromise. Neurological status was reported in all 129 pa-

ents, with neurological deficit occurring in 89 (69%), a higher value

compared with other studies. In 207 patients with spondylodiscitis, Pola et al.22 found a 23% rate of neurological deficit at the time of

diagnosis. Madhavan et al.,33 in a systematic review of 212 patients

with spondylodiscitis and end-stage renal disease, found a rate of

46% of neurological compromise. Similar to our findings, Pojskic et al.,34 in a review of 237 patients, reported 72% preoperative neuro-

ological compromise. Of note, 146 patients (61.6%) had epidural abscess at the time of diagnosis in their series. In our study, epidu-

ral abscess was found in 103 patients (79.8%).

Secondary epidural abscesses in patients with PSIs are considered

a more aggressive form of spondylodiscitis.32,35 In this regard, the same

factors that predispose patients with chronic liver disease to higher risk

of PSI could also explain more aggressive infections. In their study con-
sisting of 55 patients with spondylodiscitis, Urrutia et al.11 found that

chronic liver failure was significantly associated with the presence of

neurological compromise secondary to epidural abscess. Similar to Urru-
tia et al., our findings indicate that chronic liver disease could increase

the risk of epidural abscess and neurological compromise because liver

disease is a general risk factor for infections.32,36 These patients have in-

creased permeability at the gastrointestinal barrier system due to

changes in the intestinal flora. Moreover, the compromised neutrophil

and reticuloendothelial systems and higher rate of skin and mucous

membrane disruption due to invasive procedures (central and urinary

catheter, endotracheal intubation) can put these patients at a higher risk of bacteremia and, consequently, risk of infection.23,24,37,38

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