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Review Article

Peculiarities of spinal epidural abscess in COVID-19 patients: a literature review

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Abstract

During the SARS-CoV-2 pandemic, some authors described an increased incidence of primary Spinal Epidural Abscess (SEA) in COVID-19 patients with clinical and radiological peculiarities. Early recognition of this disease remains challenging, resulting in delayed diagnosis and significant morbidity and mortality. The authors performed a systematic review of the literature in PubMed, Cochrane, and Scopus about the traditional form of SEA comparing the main features related to COVID-19 SEA. The search was performed from 1990 to 2020. Magnetic Resonance Imaging with contrast is mandatory to recognize this kind of lesion in order to obtain a differential diagnosis. COVID-19 SEAs are generally active abscesses, with a large cystic component. Gadolinium-enhanced MR images can aid in the definition of the age and consistency of the abscess. A rim of tissue that enhances after the injection of gadolinium represents granulation tissue; liquid pus is associated with an area of low signal intensity on T1-weighted images.

This new type of SEA in COVID-19 patients showed several differences also in clinical features. No evidence of an external infective source was found (spondylodiscitis, surgery, or percutaneous treatment). None of the patients was a drug abuser and MSSA was the only responsible pathogen. The cervicothoracic spine was the most

Introduction

Spinal Epidural Abscess (SEA) is a rare infection of the spine [1], consisting of an accumulation of purulent fluid in the epidural space. The major risk factor of SEA is the active use of the intravenous drug (IVDU), followed by immunodeficiency, diabetes, obesity, and previous spinal surgery [2]. Within the spinal epidural abscesses (SEAs), there is a differentiation between SEAs related to pyogenic infectious spondylodiscitis and SEAs without neuroradiological signs of vertebral or disc infection. It is estimated that approximately 37% of patients with spondylodiscitis will develop an epidural abscess. On the other hand, primary SEAs not associated with spondylodiscitis are about 13.79% to 35.4% of all SEAs [3-5]. In fact, primary or spontaneous SEA is even rarer [1] and its recognition remains challenging due to the non-specificity of initial signs and symptoms, and several differential diagnoses [2,3]. This leads to a delayed diagnosis, with significant morbidity and mortality [6,7]. During the pandemic of SARS-CoV-2, a group in the Milan metropolitan area described an increase in the incidence of primary SEA in COVID-19 patients, not related to spondylodiscitis, with clinical and radiological peculiarities [8]. The aim of this review is to show the peculiarity of Magnetic Resonance Imaging (MRI) in primary SEA and, specifically, in COVID-19 patients. The importance of early diagnosis and treatment, reducing the significant morbidity and mortality associated, is crucial.

Materials and methods

A systematic analysis of the literature was performed using PubMed, Cochrane, and Scopus, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Studies published from January, 1st 1990

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to October, 31st 2020, in English language or at least with an English abstract, were considered for initial review. First of all, we used sequential keywords ("spinal epidural abscess"; "abscess COVID-19"), and then checked for other possibly relevant articles in references. We included clinical studies, clinical trials, observational studies, case reports, and reviews with new surgical records. We chose to exclude letters to the editor, pure reviews without new surgical records, surveys, editorials, and clinical images. A literature search was first conducted using the words "spinal epidural abscess" and "abscess COVID-19" and we found 634 articles (Figure 1). We excluded 55 studies because duplicated. Then, according to the inclusion and exclusion criteria, 98 studies have been excluded. Finally, as a result of our systematic analysis, we considered 481 articles (Figure 2).

Evidence synthesis of SEA

SEA is a quite rare condition, with a low incidence ranging from 0.2 to 2.8 per 10.000 hospital admissions [1,9-11]. Recent studies reported a mortality rate of 3.7% – 5% [6,7]. Moreover, about one-third of survivors have poor neurological outcomes [2,12,13]. The average age of patients is 63 years and the ratio of men to women is 4:1 [1,2,11]. The most relevant risk factor is IVDU with up to 53% of cases having some association and the other common risk factors are diabetes (21% - 42%) [2,14-20], human immunodeficiency virus infection (1.6% – 22%), chronic kidney or liver disease, obesity, previous spinal surgery [13,14,15,16,18]. The bacterium most frequently responsible for SEA is the *S. aureus* and particularly, Methicillin-resistant *Staphylococcus aureus* (MRSA), followed by Methicillin-sensitive *Staphylococcus aureus* (MSSA), in 43 % and 23% of cases respectively [18,20-22]. The most common mechanism of SEA is hematogenous dissemination (50%), followed by extension from contiguous infected tissues through the vertebral venous plexus (30%) and direct inoculation through the surgical procedure [2,6,23-27]. On the other hand, primary or spontaneous SEA has no evident infective source or history of trauma, surgery, or percutaneous treatment that may have violated the integrity of the spinal epidural space. This SEA is even rarer accounting for 20% of all SEAs [28-30]. The clinical presentation of SEA is specific, characterized by a triad of pyrexia, neck or back pain, and neurological deficit [15]. However, only 8% – 15% of patients have this triad [31-36]. Delayed diagnosis is in about 90% of cases [2,10,33]. The gold standard study to evaluate patients with suspected SEA is an MRI of the entire spine with contrast. The typical findings on MRI include a high signal on T2-Weighted Imaging (T2WI) and a low signal on T1-Weighted Imaging (T1WI) [3]. The enhancement can be homogenous or peripheral. The peripheral or "ring" enhancement may indicate the presence of purulent fluid, the so-called "true abscess", that is less amenable to antibiotic therapy; that is because the center of the abscess does not receive adequate vascular supply [3]. Broad differential diagnoses for SEAs include vertebral metastasis, epidural hematoma, disc disease (extruded or migrated discs), and vertebral osteomyelitis or osteodiscitis, among others. If initial imaging is nondiagnostic, and the index of suspicion for SEAs remains high, repeating radiological imaging is mandatory. There is no consensus on the optimal timing of repeating imaging studies [2]. Surgical decompression with near-to-total drainage of fluid collection, microbiological analysis, and adjuvant-targeted antibiotic therapy is the gold standard of combined treatment, in order to guarantee the best neurological recovery [18,37-40]. Nevertheless, recent systematic reviews and meta-analyses have shown that, in selected cases, only empirical, neoadjuvant antibiotic therapy can provide superimposable clinical results [41,42]. These contradictory results suggest that further research and a more detailed classification of the various subtypes of SEA are needed to clarify the outcome predictors, the indications, and the surgical timing for SEA. Postoperative recovery depends on age, health status, comorbidities, and history duration; above all, it is crucial to the patient's neurological status immediately before surgery. In the literature, there is only an article about SEA in patients with COVID-19 [8], dealing with the treatment of six patients with COVID-19 with primary SEA, during the first three months of the SARS-COV2 pandemic. We highlight the main different features of the SEA in COVID-19 patients.

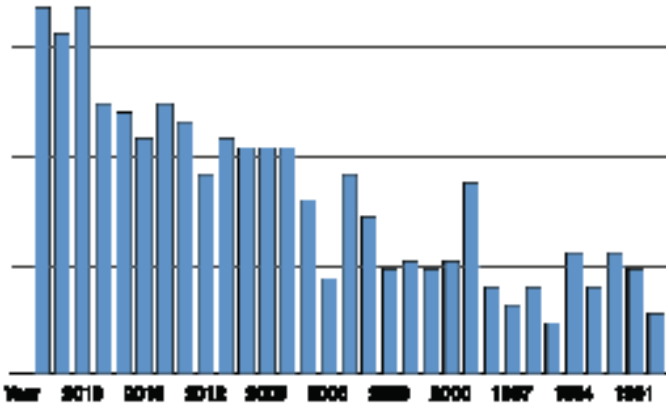

Figure 1: Graphic showing an increased number of studies about "spinal epidural abscess" from 1990 to 2020.

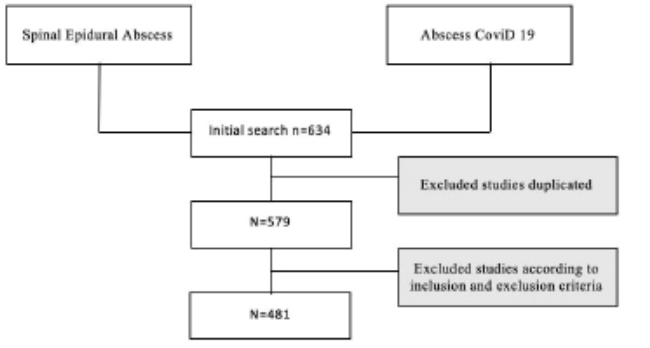

Figure 2: Study flow diagram.

Epidemiological and clinical evidence in *COVID-19 patients' SEA*

In the only article about SEA in COVID-19 patients [8,43], the authors treated six patients with primary SEA. Five of them complained of a severe form of SARS-CoV-2 infection; in one patient, the diagnosis was only based on clinical symptoms with a highly suggestive lung CT ground glass

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opacity appearance; in one case, the SEA developed once the infection was already resolved with high antibody titer; the last two patients presented an almost asymptomatic viral infection, revealed by the serologic tests [8]. These patients presented different characteristics from traditional SEA in no COVID-19 patients (Table 1). In their series, Talamonti, et al. [8] described a younger average age with a similar sex distribution (male-to-female ratio 2:1). The main difference was the fact that none of them was a drug abuser. Three were obese, two were diabetic and only one presented a moderate chronic kidney disease. Another important difference was that nobody developed any form of spondylodiscitis. MSSA was the only responsible pathogen. In three patients MSSA was also subsequently isolated in blood cultures, without clinical evidence of pyogenic infection in other body districts nor presenting signs of sepsis. Interestingly, in literature, MRSA is more frequently involved [44-46]. In this series, only one patient presented the typical onset triad with simultaneous pyrexia, neck or back pain, and neurological deficit. All patients underwent blood tests including blood culture and renal function before the MRI study. Moreover, antibiotics therapy was started according to the infectious disease evaluation. All cases were scheduled for early surgery with the aim of spinal decompression, abscess drainage, and germ isolation; we recorded one case of diffuse deep venous thrombosis with pulmonary embolism in one obese patient. The authors did not register any post-operative neurological recovery. In our experience, we did not observe a direct correlation between the occurrence of SEA and the clinical severity of COVID-19, as evidenced by the lack of a relationship between SEA and mortality. Moreover, when SEA occurred, only three patients were still fighting against active SARS-CoV-2 infection. All these patients had lymphopenia with a mild increase in white blood cell count, specifically neutrophilia; furthermore, five people had previously received immunomodulators or corticosteroids (dexamethasone) to counter the viral infection.

To date is well known that coronavirus is responsible for diffuse endothelial damage [47,48]. The authors wondered if the viral infection could have played a role in damaging the vascular endothelium, thus favoring the vascular penetration of MSSA even in the absence of a clear upper respiratory tract MSSA infection. In this way, MSSA could have reached the correspondent spinal epidural space causing progressive cellulitis of the epidural fat with the ultimate formation of the SEA. Mild immunodeficiency cannot be excluded even in the two patients who were asymptomatic for COVID-19: multiple recent clinical trials in vitro suggest that SARS-CoV-2 causes functional exhaustion of CD8 T-cells and natural killer lymphocytes due to persistent stimulation from the virus, thus inducing T-cell exhaustion. For patients with bacteremia and COVID-19, CD4, and CD8 T-cell functional exhaustion may be the reason why the MSSA can be found in the epidural space and develops a localized abscess, such as in our patients [49].

Table 1: Epidemiological and Clinical differences. IVDU (intravenous drug user); MSSA (Methicillin sensitive Staphylococcus aureus); SEA (spinal epidural abscess).

	No COVID-19 patients' SEA	COVID-19 patients' SEA
Mean age	63	54
Male:Female	4:1	2:1
IVDU	53%	0%
Pathogen	23% MSSA	100% MSSA
Clinical triad	8-15%	16%
Neurological morbidity	4-55%	100%

Radiological evidence in *COVID-19 patients' SEA*

Several differences in radiological findings were highlighted and early identification of these features is mandatory to exclude differential diagnosis and begin early treatment (Table 2). In this series, the cervicothoracic spine was the most involved site. The reason is the large fatty epidural space with a highly represented epidural venous plexus, extensively connected with both epidural lymphatics and vertebral bone veins. In our opinion, there is a significant role in developing abscesses through arterial bacteriaemia and, in this region, thanks to the redundancy of metameric radicular-medullary arteries, the vascular supply is really represented. In literature, two types of enhancement patterns are described: homogenous enhancement, which may correspond to an abscess with an inflammatory tissue in the absence of a purulent collection; and a peripheral or ring enhancement, which may indicate the presence of purulent fluid or "true abscess" [3,50,51]. The ring-enhancing abscesses are less amenable to antibiotic therapy, as the center of the abscess does not receive adequate vascular supply to treat the infection with systemic antibiotics [3,52,53]. *COVID-19 SEA* is generally active abscesses, with a large cystic component, characterized by a strong hyperintense signal on T2-weighted images with corresponding hypo intensity in T1-weighted images, suggesting a fluid content. (**Figure 3**). The cystic core is generally enclosed by a soft, fibrous capsule, characterized by high contrast enhancement after gadolinium administration, creating the pattern of enhancing ring. The authors observed that MRI with intravenous administration of

Table 2: MRI differences. MRI (magnetic resonance imaging); SEA (spinal epidural abscess).

	No COVID-19 patients' SEA	COVID-19 patients' SEA
Preferential site	Lumbar	Cervico-thoracic
Associated spondylodiscitis	30%	0%
MRI signal	Hyperintensity in T2 and hypo intensity in T1-weighted	Hyperintensity in T2 and hypo intensity in T1-weighted

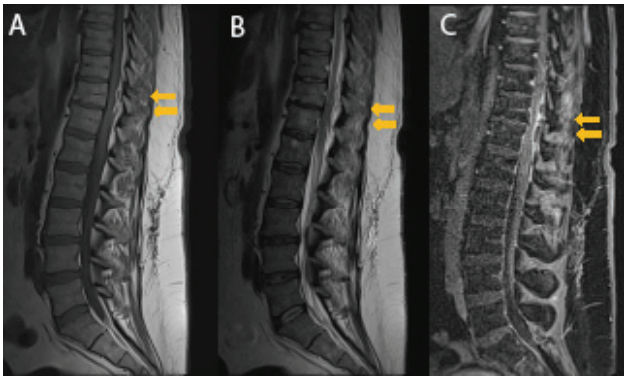

Figure 3: Spinal MRI showing an epidural MSSA abscess (Th11-Th12) in a patient with a resolved SARS-CoV-2 infection; T1-weighted acquisition (A) shows low signal images with high signal on T2-weighted image (B) and characterized by an intense contrast enhancement after Gadolinium administration (C).

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gadolinium (Gd) is more sensitive for the diagnosis of a COVID-19-related SEA. Gadolinium-enhanced MR images can aid in the definition of the age and consistency of the abscess: liquid pus is associated with an area of low signal intensity on T1-weighted images, whereas a rim of tissue that enhances after the injection of Gd represents granulation tissue [3]. COVID-19-related SEA was hyperintense relative to the surrounding tissues on diffusion-weighted MRI images and they appeared dark on apparent diffusion coefficient maps. Finally, SEA in COVID-19 patients seems to be not related to spondylodiscitis: no signs of the disc or vertebral body infectious process were observed. Moreover, no indirect signs of spondylodiscitis, such as posterior paraspinal muscle edema, psoas edema, or intervertebral disk signal abnormality, have been reported in these rare entities.

Conclusion

During the COVID-19 pandemic, a new entity of SEA was described. A high incidence of primary SEA was noticed in non-drug abuser COVID-19 patients. Since the outcome of SEA often remains poor, mainly because of delayed diagnosis and treatment, physicians should be aware that COVID-19 patients may have some greater risk of SEA than the general population. Performing an MRI with contrast is mandatory in patients with back pain and new-onset neurological symptoms. A careful study of MRI features is critical for the choice of treatment. Due to current poor evidence about SEA in COVID-19 patients, further studies are needed to validate these preliminary radiological findings.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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