Culture-negative versus Culture-positive in pyogenic spondylitis and Analysis of risk factors for relapse

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Research

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Abstract

Objectives

This study aims to compare and analyze the clinical features, diagnosis, treatment and prognosis of culture-negative and culture-positive primary pyogenic spondylitis.

Methods

A retrospective analysis of 202 cases of adult primary pyogenic spondylitis with complete clinical data in our hospital from January 2013 to January 2020 were divided into 2 groups according to the bacterial culture results: culture negative group (n = 126), culture Positive group (n = 76). Compare the clinical characteristics, diagnosis, treatment and prognosis of patients with different culture results.

Results

The culture positive rate was 37.62% (76/202). There were no significant differences in age, gender, affected segment, spinal abscess, diabetes mellitus, course of disease, surgery, recurrence, and follow-up time between the two groups (P > 0.05). Two groups of hospital admission erythrocyte sedimentation rate (erythrocyte sedimentation rate, ESR), admission C-reactive protein (C-reactive protein, CRP), admission white blood cell count (white blood cell, WBC), discharge ESR, discharge CRP, ESR decline rate, CRP There were statistically significant differences in the rate of decline, hospitalization days, and body temperature ≥ 38 °C (P < 0.05). Higher CRP levels on admission, antibiotic treatment time < 6 weeks, and body temperature ≥ 38 ℃ are independent risk factors for infection recurrence.

Conclusion

The culture-negative group's admission WBC, admission ESR, admission CRP, discharge ESR, discharge CRP, ESR decline rate, CRP decline rate, and hospital stay were lower than the culture positive group, the difference was statistically significant (P < 0.05). The independent risk factors for infection recurrence are higher CRP levels in hospital admission, antibiotic treatment time < 6 weeks, and body temperature ≥ 38 °C.

Introduction

Pyogenic spondylitis is a type of non-specific spondylitis caused by bacterial infection, mainly involving the spine and intervertebral discs. Clinically, it can be divided into a group of diseases such as discitis, vertebral osteomyelitis, and epidural abscess [1]. At present, the number of patients with purulent spondylitis has exceeded that of tuberculous spondylitis [2]. Some recent studies have found that the number of patients with purulent spondylitis with negative bacterial culture is increasing year by year [3,

4], current literature research Mostly focus on the infection around the joint prosthesis [5], and there are few studies on spondylitis with negative bacterial culture. The identification of microorganisms is the key to guiding the standardized treatment of pyogenic spondylitis. Culture-positive cases have been treated with relatively standardized treatments, among which staphylococcal inflammation is the most common [6]. Studies have reported the clinical features and results of culture-negative purulent spondylitis [7]. However, the treatment of patients with culture-negative purulent spondylitis mainly relies on empirical medication [8], and there is no established standard Treatment principles. It is increasingly important to improve the understanding and clinical treatment of culture-negative purulent spondylitis. This study focuses on the analysis of the clinical features, diagnosis, treatment and prognosis of culture-negative purulent spondylitis.

Materials And Methods

Patient selection

It is a prospective study done between 2013 and 2020. All patients' data were anonymously used. This study was approved by the Research Review Committee and the Ethical Review Committee of the Affiliated Hospital of Qingdao University. Informed consents were obtained from the patients and prior to inclusion in the study.

The study included culture-negative group (n=126), culture Positive-group (n=76) with confirmed diagnosis of pyogenic spondylitis.

Data and definitions

Inclusion criteria: (1) age ≥ 18 years; (2) the patient's clinical symptoms and imaging examinations are consistent with spinal infection; (3) histopathological examinations suggest purulent inflammation; (4) blood culture and tissue culture bacteria are positive or negative. Exclusion criteria: (1) tuberculosis, brucella, fungus and other types of spinal infections; (2) previous spinal trauma, spinal puncture and spinal surgery history.

The data analyzed include age, gender, affected segment, spinal abscess, diabetes, course of disease, whether surgery, recurrence, admission ESR, admission CRP, admission WBC, discharge ESR, discharge CRP, ESR decline rate, CRP decline rate, hospital stay, Body temperature ≥38℃.

There is no standardized antibacterial therapy. Those with positive cultures should be treated with sensitive antibiotics by drug sensitivity test, and those with negative cultures should be treated with antibiotics with broad antimicrobial spectrum. The outcome is divided into treatment success and relapse. Criteria for successful treatment: (1) Inflammation indicators (ESR, CRP) are controlled within the normal range and body temperature is normal; (2) Tissue bacterial culture is negative; (3) There is no evidence of spinal infection. The criteria for relapse are: (1) After the initial improvement, the clinical symptoms and inflammatory indicators (ESR, CRP) re-appear; (2) After the treatment is completed, the

clinical symptoms, imaging and bacteriological examinations consistent with pyogenic spondylitis appear again.

Statistical Analysis

The data results were analyzed with SPSS 20.0 statistical software. The measurement data were expressed by the mean standard deviation. When the two groups of data met the normal distribution and the homogeneity of variance, the Student t test was used, and the Mann-Whitney U rank sum test was used when the conditions were not met. Categorical variables used chi-square test, multi-categorical variables used row-multiplied list chi-square test, fisher exact test was used when the conditions of chi-square test were not met, and Mann-Whitney U rank sum test was used for ordinal categorical variables. For the risk factors with significant differences in univariate analysis, the binary logistic regression model was used to analyze. $P<0.05$ was considered statistically significant (two-sided test).

Demographics and clinical characteristics

A total of 453 patients with spinal infections were searched during the study. Among them, post-spine infection (n=46), spinal tuberculosis (n=114) and brucellosis spondylitis (n=75), spinal fungal infection (n=11), mixed spinal infection (n=5), total 251 cases. A total of 202 patients with purulent spondylitis were included in this study, of which 76 (37.62%) were culture positive. See Table 1. The culture-positive group involved 5 cases of cervical spine, 18 cases of thoracic spine, and 53 cases of lumbosacral spine. The culture-negative group involved 13 cases of cervical spine, 25 cases of thoracic spine, and 84 cases of lumbosacral spine. See Table 4.

Treatment process

Among the 202 patients in this group, 23 patients with epidural abscess were treated with emergency surgery. Tissue cultures were taken during the operation, and 16 cases were culture positive. The remaining 179 patients had complete blood cultures, and 20 were positive. The remaining 159 patients underwent CT-guided puncture of infected lesions under strict aseptic conditions, and 40 cases were positive. All patients were routinely given vancomycin + imipenem or vancomycin + fluoroquinolones or fluoroquinolones + third-generation cephalosporin antibiotics intravenously, strict bed rest, nutritional support and other conservative treatments. Those who are culture-positive should be treated with sensitive antibiotics based on the results of drug susceptibility, and those who are culture-negative will continue to be treated with broad-spectrum antibiotics, and antibiotics will be adjusted according to changes in the disease. The patient's body temperature, ESR, CRP, and WBC changes are monitored regularly. Indications for surgical treatment: Conservative treatment is ineffective, combined with spinal instability, impaired spinal cord nerve compression, and progressive symptoms. Indications for conservative treatment: conservative treatment is effective, no spinal instability, no spinal cord nerve compression damage, asymptomatic progressive aggravation, etc.

Result

Pathogenic microorganisms

There were 76 cases with positive bacterial culture, of which 43 cases were Gram-positive bacteria, and Staphylococcus aureus (n=23) accounted for the largest proportion. There were 33 cases of gram-negative bacteria, and Escherichia coli (n=16) accounted for the largest proportion. See Table 3.

Treatment outcome and relapse

The length of stay in the culture-negative group was lower than that of the culture-positive group, and the difference was statistically significant (P<0.05). There was no significant difference in the duration of antibiotic treatment and follow-up time between the two groups (P0.05). In the culture-negative group, 107 cases underwent surgery combined with antibacterial treatment, 19 cases underwent antibacterial treatment alone, and 8 cases relapsed. In the culture-positive group, 59 cases underwent surgery combined with antibacterial treatment, 17 cases underwent antibacterial treatment alone, and 10 cases relapsed. Since our hospital is a large tertiary medical center, it receives more patients with difficult and critical illnesses, patients referred by lower-level hospitals, and patients who have failed conservative treatment, so there are more surgical patients. The course of intravenous antibiotics is 2-6 weeks, and then it is changed to oral antibiotics for 4-8 weeks. See Table 2.

Risk factors associated with recurrence of infection

The variables related to recurrence of purulent spondylitis are shown in Tables 5 and 6. In univariate analysis, patients with body temperature ≥38°C, antibiotic treatment time <6 weeks, and elevated CRP showed recurrence of infection. In the multivariate logistic analysis, body temperature ≥38℃, antibiotic treatment time <6 weeks, and higher admission CRP levels were independent risk factors for infection recurrence. See Table 5 and 6.

Discussions

Pyogenic spondylitis is mainly caused by the spread of bacteria through the blood source. The arterial route is more common than the venous route. The spinal blood supply is abundant and abundant, and it is more susceptible to bacterial spread and infection [9]. In this study, we compared the clinical characteristics, diagnosis and treatment, and prognosis of the culture-positive group and the culture-negative group. We found that the inflammatory markers (WBC, ESR, CRP) of the culture-negative group were lower, and the diagnosis was often delayed. Previous studies [10] speculated that the culture-negative group had a lower pathogenic microorganism inoculation, so the signs of infection and inflammation markers It is lower than that in the culture-positive group, which is similar to the conclusion drawn by LEE YD et al. [11], which is also similar to the conclusion of KIM J et al. [12]. Studies have shown [12] that body temperature of 37.8 °C is highly correlated with infection recurrence. Our research shows that body temperature ≥ 38 °C is an independent risk factor for recurrence.

There was no statistically significant difference in diabetes between the two groups (P > 0.05), but PARK et al. studied diabetes as a risk factor for purulent spondylitis [13]. The 79 patients (79/126) in the culture-negative group clearly indicated that they had used antibiotics early and were infected with a lower dose of pathogenic bacteria. Therefore, the body can effectively exert the ability of its own immune system when it encounters a small amount of pathogenic bacteria., To respond in time to avoid greater systemic inflammation, manifested as a small increase in ESR and CRP. Research by JEAN M et al. [14] showed that taking non-steroidal anti-inflammatory drugs can also cover up clinical symptoms, leading to delays in diagnosis. After the patients in this group developed pain and other symptoms, most patients took non-steroidal anti-inflammatory drugs. Inflammation drugs and other drugs. In this study, after treatment, ESR and CRP of patients in this study showed a downward trend compared with those in hospitalization. After treatment, the rate of decline of ESR, CRP, ESR, and CRP of the culture-positive group was higher than that of the culture-negative group, and the difference was statistically significant (P < 0.05). However, the decline rate of ESR is lower than the decline rate of CRP. CRP has the characteristics of fast rise and fast decline [15]. CRP levels change significantly before and after treatment, and ESR levels fluctuate slowly and smoothly after treatment. Studies have shown [12] that higher CRP levels are associated with higher recurrence rates. Our study has similar findings that higher CRP levels are independent risk factors for recurrence.

Several studies have described the problem of the diagnosis rate of pyogenic spondylitis. In the study of HOPKINSON N et al. [10], the positive rate of blood culture was 52% and the positive rate of biopsy was 67%. In this study, the positive rate of blood culture (20/179) and the positive rate of puncture (40/159) were lower than those of open. The positive rate of biopsy (16/23) may be related to the patient's use of antibiotics before bacterial culture and the small amount of puncture specimens. According to reports [16, 17], CT-guided needle biopsy or open biopsy can improve the diagnosis rate. Based on the research of KIM C et al. [18], the author believes that there are several possible explanations for the negative culture of pyogenic spondylitis: (1) antibiotics before taking the specimen; (2) low-dose or low-grade infection; (3) False-negative biopsy of the infection site. In addition, we should also pay attention to the identification of spinal tuberculosis, brucellosis spondylitis, etc. [19].

The optimal treatment time of antibiotics has always been a controversial topic. Only one published randomized controlled trial [20] showed that 6 weeks of antibiotic treatment for pyogenic spondylitis is no less than 12 weeks, but this study excludes microbial culture Negative patients, so the results may be affected. The American Academy of Infectious Diseases believes that antibiotic treatment should last at least 6 weeks [21]. In this study, most of the total antibiotic treatment time (185/202) was 6 weeks or more. In this group of relapsed patients, antibiotic treatment time was long Less than 6 weeks. Studies have shown that treatment of less than 6 weeks is associated with an increase in the recurrence rate [12, 13]. Similarly, our research shows that the total duration of antibiotic treatment < 6 weeks is an independent risk factor for recurrence.

There is still no strong evidence to guide the use of antibiotics for culture-negative pyogenic spondylitis [20]. As Staphylococcus aureus accounts for the highest proportion in pyogenic spondylitis, KIM DY et al.

[22] suggested that when choosing empirical When antibiotics, regardless of demographic or clinical characteristics, include an effective anti-Staphylococcus aureus drug. In order to obtain a good treatment effect, it is necessary to carry out antibacterial treatment of pathogenic bacteria. Studies have shown that PCR technology can be used to detect bone and joint infections in culture-negative patients [23], thereby increasing the detection rate.

So far, there are no guidelines for conservative treatment and surgical treatment of purulent spondylitis [24]. For those patients whose conservative treatment is ineffective or whose symptoms are progressively worsening, POLA E et al. [25] and KAMAL AM et al. [26] It is recommended to use antibacterial therapy combined with surgery to treat pyogenic spondylitis. Pola et al [27] tried minimally invasive surgery to treat pyogenic spondylitis, and obtained certain clinical effects.

Conclusions

This study compared the two groups of patients before and after treatment. Before treatment, there were no significant differences in age, gender, affected segment, spinal abscess (paravertebral abscess, psoas major abscess, epidural abscess), diabetes, and course of disease between the two groups before treatment ($P > 0.05$). Before treatment, the WBC, CRP and ESR of the culture-negative group were lower than that of the culture-positive group, and the difference was statistically significant ($P < 0.05$). After treatment, there were no statistically significant differences in surgery, follow-up and infection recurrence rates between the two groups ($P > 0.05$). The culture-negative group ESR, CRP, ESR decline rate, CRP decline rate, and hospital stay were lower than the culture-positive group, the difference was statistically significant ($P > 0.05$). The decline rate of ESR in both groups was slower than that of CRP. The independent risk factors for infection recurrence are higher CRP levels in hospital admission, antibiotic treatment time < 6 weeks, and body temperature ≥ 38 °C.

Limitations

The research method is retrospective; the sample size is small, and the conclusion has certain limitations. A more credible conclusion needs to be reached in a multicenter, large sample randomized controlled trial.

Declarations

Ethics approval

This study was approved by the ethics committees of Affiliated Hospital of Qingdao University.

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

All patients involved gave written informed consent to review their medical records. All personal details were erased before analysis to cover patient data confidentiality and comply with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all of the patients for publication of this research and any accompanying images.

Availability of data and material

All the data and material can be available from Dai guohua and Wang ting for reasonable request.

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Authors' contributions

GuoHua Dai, Ting Wang, Shuzhong Li designed the study; ZhongYing Wang, LiangRui Luan ZhiChao Wang and JianWen Hou enrolled subjects and collected data; GuoHua Dai, ChuQiang Yin, YuanLian Sun analyzed the data; GuoHua Dai, Ting Wang, Shuzhong Li discussed the results and wrote the manuscript. All authors reviewed and approved the manuscript.

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Tables

Table 1. Clinical features of 202 cases of purulent spondylitis

	Culture-negative（n=126）	Culture-positive（n=76）	P
General			
Sex			1.000
male	75	45	
female	51	31	
Age,*x(_)±s*	60.89±12.21	63.28±14.95	0.218
Diabetes	11	7	1.000
Clinical feature			
Spinal pain	126	76	-
Temperature			
≥38℃	33	35	0.005
WBC（´10^9/L）x(_)±s	6.63±2.02	8.49±3.20	0.001
CRP（mg/dL）*x(_)± s*	21.373±14.549	67.62±36.22	0.001
ESR(mm/h)（*x(_)±s*	38.75±20.89	77.87±25.23	0.001
Spine level			-
Cervical	13	5	
Thoracic	25	18	
Lumbar	99	63	
Spinal abscess	51	38	0.192
Paravertebral abscess	29	18	
Epidural abscess	13	9	
Psoas abscess	9	11	
course(day)（x(_)±s	76.95±95.32	51.95±81.31	0.058

Table 2. Comparative analysis of treatment and prognosis of the two groups

	Culture-negative（n=126）	Culture-positive（n=76）	P
Laboratory			
Discharge ESR,(mm/h), *x(_)±s*	20.02±12.24	35.11±18.29	0.001
Decreased ESR,(mm/h), *x(_)±s*	18.72±13.50	42.75±18.35	0.001
Discharge CRP, （mg/dL）,*x(_)±s*	5.95±7.08	14.04±14.00	0.001
Decreased CRP,（mg/dL）,*x(_)±s*	15.44±11.44	53.55±33.14	0.001
Hospital stays（day）,*x(_)±s*	18.44±11.78	23.86±12.17	0.002
History of antibiotic use before culture	79	47	1.000
Duration of antibiotic（week）	7.13±1.341	7.42±1.594	0.173
Follow-up（month）	13.64±1.676	14.26±2.830	0.052
Surgery	107	59	0.255
Relapse	8	10	0.127

Table 3. Classification of bacteria in the culture-positive group (n=76)

Species	Values
Gram-positive	43
staphylococcus aureus	23
coagulase negative staphylococcus	8
Streptococcus	8
enterococcus faecium	3
Staphylococcus Koch	1
Gram-negative	33
E.coli	16
klebsiella pneumoniae	7
pseudomonas aeruginosa	3
salmonella	2
bacteroides fragilis	2
acinetobacter baumannii	1
enterobacter cloacae	1
Brevendimonas diminuta	1

Table 4. Spinal segment distribution of culture-negative group and culture-positive group

Levels	Culture-negative（n=126）	Culture-positive (n=76)
Cervical vertebra	13	5
C1-2	-	-
C2-3	1	-
C3-4	3	-
C4-5	3	1
C5-6	3	2
C6-7	3	2
C7-T1	-	-
Thoracic vertebra	25	18
T1-2	-	-
T2-3	1	1
T3-4	1	-
T4-5	1	-
T5-6	-	2
T6-7	2	3
T7-8	2	1
T8-9	2	-
T9-10	4	1
T10-11	3	4
T11-12	5	3
T12-L1	4	3
Lumbar vertebra	84	53
L1-2	9	9
L2-3	20	11
L3-4	25	18
L4-5	30	15
L5-S1	15	10

Table 5. Analysis of risk factors for relapse

Variable	Cure（n=184）	Relapse（n=18）	P
Age（$\bar{x}\pm s$）	61.84±12.37	61.22±21.19	0.851
Sex（male/female）	109/75	11/7	1.000
WBC（$\bar{x}\pm s$）	7.37±2.72	6.94±2.29	0.562
ESR（$\bar{x}\pm s$）	52.36±29.35	64.78±29.40	0.087
Discharge ESR（$\bar{x}\pm s$）	25.08±15.68	32.06±22.74	0.372
CRP（$\bar{x}\pm s$）	36.71±32.36	55.11±41.03	0.037
Discharge CRP（$\bar{x}\pm s$）	9.12±10.91	7.78±11.52	0.402
Course（day）（$\bar{x}\pm s$）	69.56±94.38	46.94±36.59	0.320
Temperature （$\bar{x}\pm s$）	37.94±4.29	38.25±1.17	0.542
Temperature≥38℃	53	15	0.001
hospital stays（day）（$\bar{x}\pm s$）	20.21±12.13	23.17±12.78	0.234
Spinal abscess	75	8	0.805
Culture-positive	66	9	0.307
staphylococcus aureus	19	4	0.131
E.coli	14	2	0.640
Bacteremia	17	3	0.397
Surgery	154	14	0.513
Diabetes	14	0	0.619
Other surgical or trauma history	41	5	0.565
neurological sign	77	5	0.318
History of antibiotic use before culture	113	13	0.451
antibiotic therapy（6 weeks	11	17	0.001

Table 6. Multivariate Logistic regression analysis

Variable	B	S.E	Wals(c^2)	P	Exp(B)/(OR)	95%CI
CRP	0.032	0.016	3.904	0.048	1.032	1.000-1.065
Temperature ≥38℃	2.018	0.926	4.753	0.029	7.523	1.226-46.161
antibiotic therapy□6 weeks	6.665	1.704	15.299	□ 0.001	784.278	27.803-22123.524