Admission inflammatory markers and isolation of a causative organism in patients with spontaneous spinal infection

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ABSTRACT

INTRODUCTION The purpose of this study was to investigate the significance of the inflammatory markers on admission in the isolation of a causative pathogen in patients with spinal infection. Spinal infection is treated frequently at spinal units and can encompass a broad range of clinical entities. Its diagnosis is often delayed because of the difficulty of identifying the responsible pathogen.

METHODS Patients with spinal infection treated in our institution over a period of eight years were identified and their notes studied retrospectively. Admission C-reactive protein (CRP), white cell count (WCC) as well as co-morbidities and mode of pathogen identification were recorded. Overall, 96 patients were included in the study.

RESULTS The CRP levels on admission were correlated significantly with the overall potential for isolation of a pathogen ($p<0.0001$) and positive biopsy cultures ($p=0.0016$). Admission WCC levels were associated significantly with the overall potential for isolation of a pathogen ($p=0.0003$) and positive biopsy cultures ($p=0.0023$). Both CRP and WCC levels were significantly negatively correlated with the duration of the preceding symptoms ($p=0.0003$ and $p<0.0001$ respectively). Delay in presentation was significantly negatively correlated with organism isolation ($p=0.0001$). Multivariate analyses identified the delay in presentation as the strongest independent variable for organism isolation ($p=0.014$) in cases of spontaneous spinal infection when compared with the admission CRP level ($p=0.031$) and WCC ($p=0.056$).

CONCLUSIONS In spontaneous spinal infection, delay in presentation is the strongest independent variable for organism isolation. High inflammatory marker levels on admission are a useful prognostic marker for the overall potential of isolating a causative organism either by blood cultures or by biopsy in patients with negative blood cultures. Furthermore, the admission inflammatory marker levels allow for treating surgeons to counsel their patients of the likelihood of achieving a positive microbiological yield from biopsy.

KEYWORDS

Spine infection – Culture – Inflammatory markers – Organism isolation

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Spinal infection encompasses a spectrum of disease pathologies that is inclusive of spondylodiscitis, vertebral osteomyelitis and epidural abscess.¹ The incidence of spinal infection ranges from 0.2 to 2 cases per 100,000 per year, with vertebral osteomyelitis accounting for 2–7% of all cases of osteomyelitis.^{2–4} Patient outcome after spinal infection is variable, with a poor clinical outcome following spinal infection being associated with host immunocompetence, steroid use, human immunodeficiency virus infection, multiple medical co-morbidities, methicillin resistant staphylococci and previous spinal surgery.⁴

A delay in diagnosis of spinal infection is also a significant predictor of a poorer outcome.⁵ Spinal infec-

tion tends to present insidiously, and a delay between the onset of symptoms and diagnosis is well recognised, with a reported range between 0.5 and 4 months.^{1,6,7} It is therefore evident that early diagnosis and management of spinal infection is of paramount importance in order to minimise the potential for a poor outcome.

Several authors have considered various laboratory parameters in the detection and monitoring of early surgical site infection after spinal surgery including C-reactive protein levels,^{8–10} procalcitonin,^{11,12} and granulocyte elastase.¹⁵ To our knowledge, no data exist detailing the prognostic significance of the admission inflammatory marker levels on aiding the detection and diagnosis of

spontaneous spinal infection. The purpose of this study was to investigate the prognostic significance of the admission white cell count (WCC) and the C-reactive protein (CRP) levels in relation to the potential for isolating a causative pathogen from both blood and biopsy tissue cultures.

Methods

A total of 96 consecutive patients with spinal infection presented to our unit over a period of 8 years. They were identified from admissions and discharge coding records, and were cross-referenced with the radiological, microbiological and surgical records. The 96 patients included all spinal and neurosurgical patients treated in our centre. Exclusion criteria included patients under 18 years at the time of presentation, those with postoperative spinal infections and those who had undergone previous spinal surgery.

Clinical data were gathered retrospectively from the case notes of all eligible patients. These included the presenting symptom, date of onset of the presenting symptom, age at time of presentation, date of presentation to our unit, presenting neurological status, primary source of infection and associated co-morbidities. All patients had WCC, CRP and blood culture tested on admission. The normal laboratory ranges for WCC and CRP were $4\text{--}11 \times 10^9$ cells/l and $<10\text{mg/dl}$ respectively. All patients underwent plain standing radiography and further imaging (either magnetic resonance imaging or computed tomography [CT]) was obtained in all cases.

A tissue biopsy was obtained in cases where no organism had been isolated in the initial set of blood cultures. Methods of obtaining the biopsy varied. Patients were treated with the antibiotic regimens directed by our microbiological department. Indications for surgical intervention included progressive neurological deficit, unresolving sepsis, spinal instability and persistent back pain.

Statistical analysis

SPSS® version 19 (SPSS, Chicago, IL, US) was used for statistical analysis. Comparison was made between various patient treatment pathway factors and their admission inflammatory marker values. Continuous non-parametric data were compared using the Mann-Whitney U test. Spearman correlation was used to analyse the impact of the inflammatory markers on admission with the duration of preceding symptoms. Categorical data were analysed using the Fisher's exact test.

Stepwise multiple logistical analysis of the admission inflammatory marker levels alongside the patients' baseline independent variables was also conducted, where the outcome of the model was dichotomised to either a diagnosis of infection (1) or not (0). In the model, categorical data including predisposing risk factor for infection and primary source of infection were also dichotomised in a nominal fashion to displaying the factor/source (1) or not (0) while the continuous variables of CRP level, WCC, delay in presentation and age were entered as continuous/scalar values. The significance level was defined at a p -value of <0.05 .

Results

A total of 96 patients were included (45 female [47%] and 51 male [53%]) with a mean age of 60 years (range: 21–87 years) at the time of presentation. A diagnosis of spinal infection was made in all 96 cases based on radiological, microbiological and surgical findings. A diagnosis was made of spondylodiscitis in 53, spinal abscess in 33 and osteomyelitis in 11 patients.

A predisposing risk factor associated with spinal infection was identified in 43 cases (45%): 16 diabetes mellitus, 9 intravenous drug abusers, 7 malignancies, 5 renal failures, 2 steroid or immunosuppressive therapy, 2 inflammatory bowel disease, 1 sickle cell disease and 1 liver failure. Almost half of the patients ($n=46$, 48%) had an identifiable primary source of infection: 20 wound or abscess; 8 epidural site infection; 5 urological; 4 ear, nose and throat; 4 septic arthritis; 3 endocarditis; and 2 respiratory tract. Fifty-five patients had a biopsy sample taken (27 CT guided, 19 open, 9 fluoroscopy guided, 2 lumbar punctures and 1 ultrasonography guided).

The median time between onset of symptoms and presentation was 31 days (range: 8–90 days). The median admission WCC was 10.2×10^9 cells/l (interquartile range [IQR]: $8.0\text{--}14 \times 10^9$ cells/l) and the CRP level was 78.5mg/dl (IQR: $26\text{--}197\text{mg/dl}$).

Bloods cultures were positive and isolated an organism in 32 cases (33%). A tissue biopsy was obtained in 55 patients (58%) and was positive in 35 (64%). Cultures were positive in 88% of open and 53% of closed biopsies. A causative organism was identified in 67 cases (70%) overall. No organism was identified in 29 cases (30%). Thirty patients with a positive tissue culture (86%) had a positive blood culture. The organisms isolated were: 43 methicillin sensitive *Staphylococcus aureus*, 10 methicillin resistant *Staphylococcus aureus*, 2 group B *Streptococcus*, 2 *Streptococcus milleri*, 2 Gram-positive cocci, 2 coliforms, 1 coagulase negative *Staphylococcus*, 1 group G *Streptococcus*, 1 *Streptococcus pneumoniae*, 1 *Streptococcus sanguinis*, 1 *Mycobacterium bovis* and 1 *Mycobacterium tuberculosis*.

The mean duration of treatment with antibiotics was 9.2 weeks (range: 1–110 weeks) in the 89 patients (86%) who received them. The infection was located in the cervical spine in 21, the thoracic spine in 27, the lumbar spine in 42 and at multiple levels in 6 cases. Three-quarters of the patients ($n=72$, 75%) underwent surgical intervention: 40 decompression, and 32 decompression and fusion. A quarter of the patients ($n=24$, 25%) required no surgical intervention and were managed conservatively.

The CRP levels on admission were correlated with the duration of preceding symptoms ($p=0.0003$), with organism isolation by either blood or tissue culture ($p<0.0001$) and with organism isolation from biopsy alone ($p=0.0016$) (Table 1). Admission WCC was correlated with the duration of preceding symptoms ($p<0.0001$), organism isolation by either blood or tissue culture ($p=0.0003$) and organism isolation from biopsy alone ($p=0.0023$) (Table 1). Admission levels for both CRP and WCC were negatively correlated with the duration of preceding symptoms ($p=0.0003$ and $p<0.0001$ re-

Table 1 Univariate analysis of admission inflammatory marker levels and patient treatment pathway factors

Predictor	Organism isolated (n=67)	No organism isolated (n=29)	p-value
Male-to-female ratio	38:29	13:16	0.374*
Age at time of presentation (IQR) in years	61 (49–73)	66 (50–70)	0.538**
Ratio of identifiable source of infection to no identifiable source	34:33	12:17	0.505*
Delay between onset of symptoms and presentation (IQR) in days	17 (7–50)	93 (45–134)	0.0001**
Admission CRP (IQR) in mg/dl	131 (35–207)	27 (8–40)	<0.0001**
Admission CRP and chance of organism isolation from biopsy (IQR) in mg/dl	94 (30–185)	19 (7–47)	0.0016**
Admission WCC (IQR) in x 10 ⁹ cells/l	11.9 (9.1–15.6)	8.6 (7.7–10.4)	0.0003**
Admission WCC and chance of organism isolation from biopsy (IQR) in x 10 ⁹ cells/l	12.5 (9.0–16.0)	8.9 (7.1–9.6)	0.0023**

IQR = interquartile range; CRP = C-reactive protein; WCC = white cell count

*Fisher's exact test; **Two-tailed Mann–Whitney U test

Table 2 Analysis of the predictive value of admission inflammatory marker levels in patients with spinal infection. (Organism identification from either blood culture or biopsy)

	Isolation of an organism with increased CRP	Isolation of an organism with increased WCC
Sensitivity	37.0%	88.9%
Specificity	98.5%	54.4%
PPV	90.9%	43.6%
NPV	79.0%	92.5%
Likelihood ratio	24.10	1.95
p-value*	<0.0001	0.0001

CRP = C-reactive protein; WCC = white cell count; PPV = positive predictive value; NPV = negative predictive value

*Fisher's exact test

Table 3 Analysis of the predictive value of admission inflammatory marker levels in patients with spinal infection. (Organism identification from biopsy alone)

	Positive biopsy with raised CRP	Positive biopsy with raised WCC
Sensitivity	100%	87.0%
Specificity	67.4%	55.3%
PPV	36.4%	58.8%
NPV	100%	84.2%
Likelihood ratio	3.10	1.86
p-value*	0.0005	0.0035

CRP = C-reactive protein; WCC = white cell count; PPV = positive predictive value; NPV = negative predictive value

*Fisher's exact test

spectively.) As a result, patients with a higher CRP and/or WCC on admission had preceding symptoms for a shorter period than those with lower inflammatory markers. Furthermore, the chance of isolating an organism from either blood or tissue culture or from biopsy alone was greater in patients with higher admission inflammatory marker levels.

Stepwise multiple logistic analyses concurred with the univariate analysis, identifying age, predisposing risk

factor for infection and primary source of infection as non-significant variables. The final model inclusive of the independent variables, admission CRP and WCC, and delay in presentation had an R² value of 47%. This statistical model showed that delay in presentation ($p=0.014$) was the most significant factor in identifying an organism in cases of spontaneous spinal infection, followed by admission CRP ($p=0.031$) and, finally, admission WCC, which was not quite significant ($p=0.056$).

The admission CRP level for identifying an organism overall (from either blood or biopsy) was highly specific (99%), indicating that a pathogen was extremely unlikely to be identified in the absence of an elevated CRP level ($p<0.0001$). In contrast, for organism identification from biopsy alone, the admission CRP level proved highly sensitive (100%), indicating that the CRP level was elevated in all cases of a positive biopsy culture ($p=0.0005$).

The admission WCC for identifying an organism overall (from either blood or biopsy) and from biopsy alone were highly sensitive (89% and 87% respectively), indicating that a pathogen was likely to be identified in the presence of an elevated CRP level ($p=0.0001$ and $p=0.0035$ respectively). Tables 2 and 3 summarise the predictive values for the admission inflammatory marker levels on isolating a causative organism overall and from biopsy alone.

Discussion

This study examined 96 patients who were diagnosed and treated for a spontaneous spinal infection at our unit. The results demonstrate a statistically significant positive correlation, for both admission CRP and WCC levels, with achieving a positive microbiological culture from either blood or biopsy cultures. The results also showed a negatively correlated microbiological yield with the duration of preceding symptoms in that patients who presented later were less likely to achieve a microbiological culture by any means.

In spinal infection, a delay between the onset of symptoms and diagnosis is well recognised, and has been attributed historically to the insidious nature of the condition.⁴ Multiple studies have demonstrated the correlation between the CRP level and the severity of infection.^{14–16} In this study, the findings from the univariate analysis showed that the duration of preceding symptoms was correlated negatively with the chances of isolating a causative organism, suggesting that CRP quite accurately mimics the severity of infection in spinal infection in that patients with less severe infection appeared to present later.

However, the results of the multiple logistic analyses identified that delay in presentation was an independent variable in terms of organism isolation in cases of spontaneous spinal infection from the admission inflammatory marker levels. Furthermore, delay in presentation was identified as the most significant independent variable ($p=0.014$) measured in this study for guiding surgeons to the likelihood of identifying an organism in cases of spontaneous spinal infection.

In several studies, WCC, CRP and erythrocyte sedimentation rate (ESR) have been shown to increase in patients with spinal infection.^{17,18} CRP is a plasma protein that is a part of the systemic response to inflammation, increasing rapidly after tissue injury or infection.¹⁹ The ESR is the rate at which red blood cells sediment in a period of one hour and represents a non-specific indirect measure of inflammation.²⁰ CRP rises faster than the ESR in acute infection, and is considered to be a more specific and sensitive

inflammatory marker for the diagnosis and monitoring of treatment for patients with infections, including spinal infection.^{17,20–22}

The importance of admission inflammatory CRP in the diagnosis of spinal infection is demonstrated in our study as elevated levels were correlated positively with achieving a positive culture, from either blood or biopsy samples. Other studies have shown the WCC is not always high and an elevated CRP level is a stronger indication of the presence of spinal infection.^{23,24} The univariate results of the present study showed that an elevated WCC is also correlated positively with achieving a positive culture but the multivariate analyses concurred with previous authors' findings, showing the admission CRP levels to be related more strongly to the chances of organism isolation ($p=0.031$) than the admission WCC levels, which were not quite significant ($p=0.056$). Although admission inflammatory marker levels are conducted routinely, these findings provide the treating surgeon with supporting evidence of the likelihood of achieving a positive culture.

To date, the prognostic significance of admission inflammatory markers for organism isolation in spinal infection has not been established. This study demonstrates that admission CRP and WCC are highly specific and sensitive for the potential of isolating a causative organism in patients. Considering the combination of admission CRP and WCC is useful as admission CRP is a highly specific test (99%) while admission WCC is a highly sensitive test (89%).

In spinal infection, an organism may not be isolated in up to a third of cases.² The results of the present study should encourage the treating orthopaedic surgeon that high levels of admission WCC and CRP indicate an increased potential for isolating a pathogen, and furthermore allow the treating surgeon to counsel his or her patients regarding the likelihood of yielding a positive biopsy result. This is important considering the invasive nature of undergoing CT guided biopsy that is commonly necessitated in cases where a blood culture is negative and operative intervention for drainage, decompression or stabilisation is not initially indicated.

To our knowledge, this is the first study addressing the correlation of WCC and CRP with the potential for isolating a causative pathogen in cases of spontaneous spinal infection. The large number of cases allowed for statistically significant outcomes to be elicited. The main limitation of our study is its retrospective nature.

Conclusions

We report our experience with 96 cases of spinal infection. Our results have identified that the strongest measured independent variable affecting organism isolation in cases of spinal infection was the delay in presentation to our unit. Our findings also demonstrated that the admission inflammatory marker levels were correlated positively with achieving a positive microbiological diagnosis in cases of spontaneous spinal infection. The admission CRP levels are a stronger independent variable than the admission WCC for organism isolation in cases of spontaneous spinal

infection. The combination of the admission WCC and CRP is a highly sensitive and specific test for the isolation of an organism in patients with spinal infection.

The inflammatory marker levels are also of significant prognostic value for isolating an organism, from blood or biopsy culture, in case of spinal infection. Furthermore, the admission inflammatory marker levels help guide the treating surgeon to counselling his or her patients as to the likelihood of yielding a positive biopsy culture in cases of spinal infection.

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