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Development of Criteria Highly Suggestive of Spinal Tuberculosis

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BACKGROUND: **In a developing country there is a need for development of criteria that can be used for the diagnosis of spinal tuberculosis, which is common in that region.**

METHODS: **Demographic, clinical, and radiologic features of spinal tuberculosis and spinal epidural tumors have been compared statistically, and inferences have been drawn in terms of *P* values, sensitivity, specificity, positive predictive values, and negative predictive values.**

RESULTS: **A statistically significant relationship was found between spinal tuberculosis and spinal pain, fever, gradually progressive lower limb weakness, contrast-enhancing epidural ± paravertebral lesions, continuous levels affected, spinal deformity, and raised erythrocyte sedimentation rate.**

CONCLUSIONS: **These relationships were considered the most probable criteria for the diagnosis of spinal tuberculosis.**

INTRODUCTION

In tropical and developing countries, tuberculous infection is a major cause of morbidity and mortality.[1] Epidemiologically, spinal tuberculosis (STB) accounts for 15% of the total extrapulmonary cases of tuberculosis (TB) and approximately 2% of total cases of TB.[2]

Despite progress toward TB elimination, it is still an area of public health concern in the developing world. In the 2017 World Health Organization Global Tuberculosis Report, the global incidence of TB was measured at 61%, which accounts for 6.3 million new cases. The largest incidence of TB was reported in the countries of South and Southeast Asia. Furthermore, the study identified low-income countries as having a higher incidence of TB, which in turn led to higher mortality due to this infection. The report also found that the majority of deaths due to TB could be prevented by timely diagnosis and early treatment.[3] As mentioned earlier, spinal TB accounts for 15% of extrapulmonary tuberculosis, which makes it an area of considerable interest.

In moving toward reducing morbidity and mortality associated with this disease, timely diagnosis of spinal TB plays an important part. Delay in the diagnosis and treatment of STB can result in spinal cord compression and spinal deformity, which significantly affects the quality of life of patients.[4] The incidence of spinal TB has increased even in developed parts of the world. An increase in cases of spinal TB from 14% to 45.2% among foreign-born residents in Barcelona, Spain over a period of 10 years and a prevalence of 0.05 cases per 100,000 in the United States in 2011 have been reported.[5,6]

Neoplasms are another group of diseases that commonly affect the spine. Primary tumors of spine are rare[7] and 10 times less common than intracranial tumors. Therefore as most of the data suggest, these lesions are metastatic deposits that arise commonly from lung and breast cancers.[8,9] The area most commonly affected within the spine by this disease is the vertebral bodies followed by paravertebral structures.[10]

Clinically, STB has suggestive signs and symptoms. The study by Garg et al[11] identified a set of clinical and radiologic features, which they found to be specific for patients diagnosed with STB. These features included symptoms of back pain, spinal tenderness, and paraplegia, whereas radiologic features included destruction of intervertebral disk and vertebral bodies and presence of spinal deformity.[11]

Key words
- Diagnostic criteria
- Erythrocyte sedimentation rate
- Spinal deformity
- Spinal TB

Abbreviations and Acronyms
CRP: C-reactive protein
ESR: Erythrocyte sedimentation rate
MRI: Magnetic resonance imaging
STB: Spinal tuberculosis
TB: Tuberculosis

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The definitive diagnosis of STB, however, is based on laboratory and histopathologic investigation. Examples of pathologic tests are tuberculin tests, histopathology of any tissue obtained, and microbiologic culture of the mycobacterium.[4,12,13]

Radiologic examinations are a further necessary diagnostic step in evaluating spinal pathologies. Among these, magnetic resonance imaging (MRI) examination is the preferred modality.[14-16] For spinal tumors, it can assist in identifying and differentiating between different types of tumors. Some articles, such as one by Arima et al,[17] suggest that MRI can do this task with an 89% accuracy. For spinal TB, MRI scans show distinct vertebral epidural involvement and inflammatory changes.[18]

With the incidence of spinal TB on the rise, it has become pertinent that a timely and quick diagnosis of this disease is made so that treatment of patients can be started and the significant burden of health expenses on patients living in the developing countries can be reduced. Keeping up with this intent, our paper aims to identify certain clinical, radiologic, and laboratory features for STB and compares it with those of spinal tumors.

METHODOLOGY

Our study is an audit-based review and analysis of cases that presented and were consequently treated as inpatients at Aga Khan University & Hospital in Karachi, Pakistan from 2011 to 2016. Patient medical record numbers were taken using the hospital's human information management systems. The sample size was calculated, and the sampling technique of our study was nonprobability.

Information regarding history and examination findings was then obtained from individual medical records of the patients, whereas radiologic and laboratory results were obtained from the hospital's clinical record system.

Inclusion Criteria

We included patients characterized by the following:

- Treated during the period mentioned
- Treated as inpatients
- Undergoing a procedure during which sample(s) for pathology was/were obtained
- With complete medical records
- With available gadolinium-enhanced MRI
- With laboratory data leading to a pathologic diagnosis of either TB or tumor

An ethical review committee exemption was obtained before the start of the study, following which the proforma to retrieve information was developed using the Epidata Manager Version 4.0 and data entry was done using Epidata Entry Client version 4.0.

The proforma included demographic patient information such as medical record number, age, and gender. Basic patient information such as body mass index, comorbids, and bacillus Calmette-Guerin vaccination status was also recorded.

As shown in **Table 1**, clinical signs and symptoms included the presence or absence of pain, neurologic deficits, fever, tenderness, and spinal deformity. Mode of onset was described as acute for signs and symptoms manifesting in ≤14 days and chronic for ≥15 days. Pain scale was noted on a scale of 1–10. Fever was further explored as high grade, low grade, with chills, whereas neurologic deficits were further divided as motor and/or sensory and whether they were present in upper and/or lower limbs. Clinical investigations include total leukocyte count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values at the time of disease.

Table 1. Demographic and Radiological Features That Were Recorded for Each Case

1. Age
2. Gender
3. Comorbids
4. Onset
5. Pain
6. Fever
7. Neurologic deficit
a. Upper limb motor
b. Lower limb motor
c. Upper limb sensory
d. Lower limb sensory
8. Spinal deformity
9. TLC
10. ESR
11. CRP
12. Vertebral erosion
13. Posterior element erosion
14. Epidural lesion*
15. Paravertebral lesion*
16. Continuous levels
17. Noncontinuous levels
18. Deformity

TLC, total leukocyte count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
*Contrast enhancing.

Radiologic features included vertebral body and posterior element erosion and epidural and paravertebral components, which were further divided into contrast enhancing and noncontrast enhancing. The affected spinal region was also noted and divided into 7 categories, namely cervical, thoracic, lumbar, sacral, cervicothoracic, thoracolumbar, and lumbosacral. The diseased numbers of continuous and noncontinuous spinal levels were noted, and, finally, any spinal deformity such as kyphosis, scoliosis, and kyphoscoliosis were recorded.

Exclusion Criteria

Any patient with incomplete clinical, radiologic, and pathologic information (as defined in the inclusion criteria) was excluded.

Table 2. Summary of Descriptive Frequencies and Statistical Analyses of Data

	Spinal Tumor Number (%)	Spinal TB Number (%)	*P* Value
Gender			
1. Male	31 (62)	20 (40)	
2. Female	19 (38)	30 (60)	
Onset			
1. Acute	18 (36)	11 (22)	
2. Chronic	31 (62)	39 (78)	
Pain	32 (64)	42 (84)	0.023
Fever	2 (4.0)	10 (20)	0.014
Neurologic deficit	32 (64)	27 (54)	0.309
1. Upper limb motor	5 (10)	5 (10)	1.000
2. Lower limb motor	36 (72)	34 (68)	0.663
3. Upper limb sensory	2 (4.0)	0	0.153
4. Lower limb sensory	13 (26)	9 (18)	0.334
Spinal region			0.721
1. Cervical	3 (6.0)	2 (4.8)	
2. Dorsal	13 (26)	23 (46)	
3. Lumbar	11 (22)	12 (24)	
4. Sacral	0	0	
5. Cervicodorsal	1 (2.0)	1 (2.0)	
6. Dorsolumbar	3 (6.0)	4 (8.0)	
7. Lumbosacral	1 (2.0)	0	
Vertebral body erosion	39 (78)	45 (90)	0.102
Posterior element erosion	26 (52)	20 (40)	0.229
Epidural lesion	33 (66)	44 (91.7)	0.002
Paravertebral lesion	22 (44)	40 (83.3)	0.000
Continuous levels			0.002
1. Two	14 (28)	32 (64)	
2. Three	5 (10)	6 (12)	
3. Four	2 (4.0)	1 (2.0)	
4. Five	4 (8.0)	0	
Noncontinuous levels			0.018
1. One	20 (40)	7 (14)	
2. Two	0	1 (2.0)	
3. Three	3 (6.0)	0	
4. Four	1 (2.0)	2 (4.0)	
5. Five	1 (2.0)	2 (4.0)	
6. Six	0	0	
Deformity			0.503
1. Kyphosis	1 (2.0)	2 (4.0)	
2. Scoliosis	0	0	
3. Kyphoscoliosis	0	1 (2.0)	
ESR	15.2	37.1	0.028
CRP	11.5	12.5	0.896

For all results, *P* value was considered significant at <0.05 with a confidence interval of 95%.
TB, tuberculosis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

The equal number of cases in both arms (i.e., 50 cases of STB and 50 cases of spinal tumors) made it easier to draw a comparison.

STATISTICAL ANALYSES

Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS version 21). Descriptive analysis of categorical data was shown in terms of frequencies and percentages, whereas that for continuous variables was presented as mean ± standard deviation. The Pearson chi-squared test was used for comparing categorical variables wherever applicable. The confidence interval of our study was 95%, and a P value <0.05 was considered significant. Positive and negative predictive value pertinent variables, along with their specificity and sensitivity, were also calculated.

RESULTS

The mean age of patients diagnosed with spinal TB was 46.20 (S.E ± 2.8). More than half (60%) of the patients were female with 78% presenting with chronic onset of symptoms. Within clinical signs and symptoms, pain was reported by 42 (84%) cases, fever by 10 (20%), and neurologic deficit by 27 (54%) cases. Within neurologic deficits, reported cases of motor weakness in upper limbs and lower limbs were 5 (10%) and 34 (68%), respectively. Sensory symptoms were only noted for lower limbs in 9 (18%) of the cases. For all STB cases, the reported mean ESR was 37.17 (S.E ± 5.4) and CRP was 12.54 (S.E ± 3.8). Statistics for radiologic features of cases showed 45 of them (90%) had vertebral body erosion and 20 of them (40%) had posterior element involvement. Cases that had contrast-enhancing epidural lesions were 44 (91.7%), and contrast-enhancing paravertebral lesions were 40 (83.3%) after adjusting for missing values. Two continuous levels were affected in 32 (64%), whereas 1 noncontinuous level was affected in 7 of the cases (14%).

For patients with spinal tumors, the mean age was 48.66 (S.E ± 2.6). Thirty-one (62%) of the patients were male. Within clinical signs and symptoms, pain was reported by 32 (64%) cases, fever by 2 (4%), and neurologic deficit by 32 (64%) cases. Within

neurologic deficits, reported cases of motor weakness in upper limbs and lower limbs were 5 (10%) and 36 (72%), respectively. Sensory symptoms in upper limbs and lower limbs were 2 (4%) and 13 (26%), respectively. For all spinal tumor cases, the reported mean ESR was 15.21 (S.E ± 4.7) and CRP was 11.51 (S.E ± 5.5). Statistics for radiologic features reported for cases showed 39 (78%) had vertebral body erosion and 26 (52%) had posterior element involvement. Cases that had contrast-enhancing epidural lesions were 33 (66%), and contrast-enhancing paravertebral lesions were 22 (44%). Two continuous levels were affected in 14 (28%), whereas 1 noncontinuous level was affected in 20 (40%) of the cases.

Using the Pearson chi-squared test, categorical variables that were statistically associated with STB and spinal tumor were identified. Within clinical signs and symptoms, pain and fever were significantly associated ($P < 0.05$) with STB, whereas for radiologic factors, contrast-enhancing epidural and paravertebral lesions and affected continuous levels were significantly associated ($P < 0.05$) with STB. The only feature that was significantly associated ($P < 0.05$) with spinal tumors was affected noncontinuous spinal levels. We also found statistically significant differences for ESR values between 2 groups ($P < 0.05$). These findings are summarized in Table 2. We also measured the sensitivity, specificity, positive predictive value, and negative predictive value of significant variables in relation to spinal tuberculosis which are shown in Table 3.

Table 3. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Significant Variables in Relation to Spinal Tuberculosis

Signs and Symptoms	Sensitivity	Specificity	PPV	NPV
1. Back pain	56.7%	69.2%	84%	36%
2. Fever	83.3%	43.9%	54%	36%
3. Spinal deformity	50%	50%	5%	95%
4. Gradually progressive lower limb weakness	48.5%	46.6%	68%	28%
5. Sensory deficit of lower limb	40.9%	47.4%	16%	74%
6. Sphincter control deficit	47.5%	46.1%	84.7%	12.2%

DISCUSSION

In developing countries, tuberculous (TB) infections are still prevalent with a varied set of manifestations. Within the past few decades, a resurge of TB cases has been seen in the developing world.[19] Among TB infections, 2% affect the vertebral column.[2] A study done in India showed that 30% of nontraumatic paresis was due to STB.[13] Keeping in mind that the risk factor profile for TB in South Asian countries is similar to each other, the results of this study can be extrapolated to Pakistan to suggest that STB is highly prevalent in the country. Coupled with the emergence of multidrug-resistant strains and predominance in human immunodeficiency virus–infected patients,[20] STB is a debilitating disease that, if left untreated, could severely impair the quality of life of patients.

The study done in India also found that spinal tumors comprised 10% of the cases that presented with nontraumatic paresis. As established, primary spinal tumors are rare[21] and most cases are found to be metastatic deposits of primary tumors of other parts of the body. A small number, 5%–10%, of these deposits are found in the epidural space and, if not treated, can cause significant neurologic damage[22] including paralysis and loss of sphincter control.[23] Therefore early diagnosis and prompt treatment can provide significant benefit in terms of the neurologic outcome for patients with spinal tumors.[24]

For spinal tuberculosis and spinal tumors, clinical judgment based on signs and symptoms of patients, correlated with specific radiologic imaging, could greatly improve the accuracy of diagnosis, eventually leading to a faster and better treatment process.[20] However, for the purposes of our study, we focused on establishing criteria based on clinical and radiologic features of spinal TB.

In our study, we included 50 cases of STB and spinal tumors each, conducting an audit of major clinical and radiologic features that were seen in these patients. The mean age was found to be similar in both diseases, close to the end of the fourth decade of life. On an overall glimpse, most of the patients in both groups presented with overlapping clinical characteristics; however, the spinal tuberculous patients had a more insidious onset of symptoms.

The major clinical feature presenting in both diseases was pain. This symptom, however, was higher in percentage in patients with STB (84%) as compared with those with spinal tumors (54%). Twenty percent of the patients with STB reported fever as a symptom, whereas it was found among only 4% of cases of spinal tumors.

Clinical laboratory tests were limited to recording of total leukocyte count, ESR, and CRP measurements. On literature review, most studies did not mention these laboratory values as a part of their diagnostic process. In our study, laboratory values had a larger standard deviation and were not clinically significant. Therefore these variables were not considered as part of the final criteria.

The dorsal region of the spine was most affected in STB, with 51% of the lesions presenting in this area. This is similar to another study in which the results also showed a greater involvement of the thoracic spine in STB.[4]

Vertebral body erosion was commonly seen in 1 study by De Backer et al.[19] Our study also showed similar findings as we encountered vertebral body erosion in 90% of our patients. STB lesions showed significant postcontrast enhancement in the epidural and paravertebral regions. This is similar to a study conducted in France, where 77% of cases had epidural involvement.[16]

Under the guidance of our senior author (G.J.), 2 types of criteria have been developed to diagnose spinal tuberculosis.

Using the results of statistical analysis, we divided the features into 2 categories, namely most probable and possible for STB. The most probable features were those that had a statistically significant association with the disease and were verified by other statistical tests. Possible features were those that did not show a statistically significant association with a disease but, based on descriptive frequencies, could be linked to the disease.

Most probable diagnostic criteria for STB:

- Pain
- Fever
- Gradually progressive lower limb weakness
- Contrast-enhancing epidural and paravertebral lesions
- Continuous (contiguous) levels affected
- Spinal deformity
- Raised ESR

Possible diagnostic criteria for STB:

- Female gender
- Presence of vertebral body erosion on radiologic findings

What makes this study noteworthy is the fact that it attempts to compare the overlapping features that can be found in both spinal tumors and spinal TB. Although numerous studies have been done to identify such features, they look at both pathologies individually rather than drawing a comparison between the 2. Our study aims to do the latter. This is helpful in drawing out criteria that can be used for diagnosis and detection of spinal tuberculosis. It holds particular importance in developing countries, where resources are limited and numerous investigations can increase the burden on the health system to make a final diagnosis. With a set of criteria in hand, clinicians would find it easier to approach such patients in a way that is not only cost effective but also accurate.

Our study, however, has few limitations as it is a retrospective study with a relatively smaller sample size. Therefore we intend to conduct a prospective study with a larger sample size to validate our results.

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