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Diagnosis of Tuberculous Spondylitis in Current Medical Practice

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Abstract The study was based on the results of the examination and treatment of 75 (100%) patients diagnosed with tuberculous spondylitis (TS). The patients' ages ranged from 20 to 80 years, with an average age of 52 years. There were 35 men (46.7 ± 0.58%) and 40 women (53.3 ± 0.58%). Additionally, a comparison group of 50 (100%) patients (21 men (42 ± 0.7%) and 29 women (58 ± 0.7%)) diagnosed with pyogenic spondylitis (PS), aged 25-77 years, with an average age of 58 years, was studied. Highly suggestive MRI and CT signs of TS and their prevalence were as follows: thoracic spine involvement in 50.7%, involvement of more than two vertebrae in 22.7%, vertebral body collapse in 36%, involvement of the vertebral pedicles in 9.3%, unclear boundaries of the destruction cavity in 58.7%, sequestrum in 10.6%, and subligamentous abscess spread to two or more vertebrae in 25.3%. The sensitivity, specificity, and positive predictive value of P1NP serum elevation for the differential diagnosis of TS and PS were 84.2%, 62%, and 95.2%, respectively. In 12 (16 ± 0.4%) patients with negative QFT results, tuberculous spondylitis was confirmed histologically in 3 (4 ± 0.23%) patients, bacteriological confirmation was obtained in 7 (9.3 ± 0.33%) patients, and both histological and bacteriological confirmation was obtained in 2 (2.7 ± 0.19%) cases.

Keywords Tuberculous spondylitis, Pyogenic spondylitis, Quantiferon TB Gold

1. Introduction

In the Republic of Uzbekistan, bone and joint tuberculosis has the highest incidence rate among cases of extrapulmonary tuberculosis. Tuberculous spondylitis (TS) represents 80% of all musculoskeletal tuberculosis cases [12]. The most severe complications of TS include paresis, paralysis, and dysfunction of the pelvic organs, with up to 60% of cases leading to a lasting loss of functionality despite treatment with anti-tuberculosis medication, pathogenetic therapy, and surgery [1]. Pathogenetically, the destruction of the vertebra in TS occurs as a result of the formation of infectious granulomas after hematogenous dissemination of Mycobacterium tuberculosis into the blood-rich spongy bone of the vertebral bodies, and the progression of the disease is manifested by the occurrence of caseous necrosis of the growing granuloma, exudation, increased cytokine activity, which activates osteoclasts [5,17].

Diagnosing TS is challenging because the early stages of the disease present with a vague clinical picture. As a result, even primary medical doctors rarely order an MRI of the affected spine segment, except in rare cases, since pain is reflected muscle pain. Only after several months or more, after the destruction of the spinal motor segment, instability and neurological symptoms appear, the general condition of the patient worsens, at this stage, depending on the visual signs, a diagnosis of spondylitis, pathological fracture, spondylopathy or even metastasis is established [17]. For differential diagnosis in these cases, a percutaneous trephine biopsy of the affected vertebra is recommended. The sensitivity of this procedure in detecting tuberculous inflammation is generally no more than 60%, depending on the patient population.

The diagnostic process for patients suspected of having tuberculosis includes tuberculin testing, which is used to assess the body's specific sensitivity to Mycobacterium tuberculosis. Currently, tuberculin skin tests (Mantoux test, Diaskintest etc.) and IGRA test (Quantiferon TB Gold, Wantai TB- IGRA) are used. However, current diagnostic methods for TB infection (TST, IGRA, and TBST) have a variety of limitations. The IGRA cannot distinguish between active tuberculosis and latent tuberculosis infection, and the TBST is limited by the same problem [13].

2. Purpose

To determine the capabilities of laboratory, radiological and immunological tests in the diagnosis of TS.

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3. Materials and Methods

The study was based on the results of examination and treatment of 75 (100%) patients diagnosed with TS. The age of the patients ranged from 20 to 80 years. The average age was 52 years. There were 35 men (46.7 ± 0.58%), 40 women (53.3 ± 0.58%). In addition, a comparison group of 50 (100%) patients (21 (42 ± 0.7%) - men, 29 (58 ± 0.7%) - women) diagnosed with pyogenic spondylitis (PS), aged 25-77 years, the average age was 58 years, was studied. Patient examination was conducted through general clinical assessments and specialized laboratory tests, based on their symptoms and medical history on the Biossays 240 Plus biochemical analyzer (Snibe Diagnostic, Shenzhen, China) and Finecare™ FIA Meter Plus, Wondfo Biotech (Guangzhou, China), chest X-ray (CT was performed as indicated), ultrasound examination of internal organs on the Siemens Acuson device (Berlin, Germany), ECG on the BTL-08 SD device (in the older age group, an echocardiogram was performed on the Siemens Acuson device (Berlin, Germany).

During a general examination, the presence and number of BCG revaccination scars were determined.

After the orthopedic examination, MRI (MRI SIGNA HD / e, 1.5 Tesla, General Electric, USA) and CT (Siemens Definition AS 64, Germany) were performed to study the affected segment of the spine.

Bone metabolism was studied by determining the bone formation marker - P1NP (N-terminal telopeptide) in the blood serum on an automatic electrochemiluminescent immunoassay analyzer Cobas e 411 (Roche Diagnostics, Switzerland).

All patients were tested using the Quantiferon TB Gold (QFT) laboratory test to detect tuberculosis infection. This test identifies INF-γ (gamma interferon) released by sensitized T cells, which are stimulated in vitro by specific proteins (ESAT -6, CFP-10, TB7.7 (p4)) from Mycobacterium tuberculosis, a part of the Mycobacterium tuberculosis complex.

Tissue samples collected during surgical procedures were fixed in formalin, stained with hematoxylin-eosin and cut with a microtome, then examined under a microscope. The presence of central necrosis surrounded by epithelioid and Pirogov-Langhans cells confirmed tuberculous inflammation of the spine.

Pathological tissues and fluids obtained during surgeries, punctures, fistula drainage, and sputum were examined bacteriologically. Molecular genetic methods used included GeneXpert® MTB/Rif (Sunnyvale, California, USA) and GenoType MTBDRplus (Hain Lifescience GmbH, Nehren, Germany). Mycobacterial culture growth was assessed using the BACTEC MGIT 960 medium (Becton Dickinson India Pvt. Ltd., Gurgaon, India) and cultured on solid Lowenstein-Jensen medium. The tuberculosis diagnosis was made based on a developed evaluation algorithm based on clinical, laboratory, and tomographic data, scored in points.

A combination of isoniazid (H) 75 mg, rifampicin (R) 150 mg, ethambutol (E) 275 mg, and pyrazinamide (Z) 400 mg fixed-dose anti-tuberculosis drugs was prescribed for 3 months, followed by H and R for 10 months. According to body weight, 3 tablets (less than 55 kg), 4 tablets (over 55 kg), or 5 tablets (over 70 kg) were administered daily. In cases of drug resistance to H and R, levofloxacin 1000 mg, linezolid 600 mg, clofazimine 100 mg, and cycloserine 750 mg were given daily, along with bedaquiline 200 mg three times a week (after 14 days, 400 mg daily) for 22 months.

Statistical analysis of the study was carried out using modern computer systems such as IBM/PQ of the latest generation using a package of standard Excel programs.

4. Results

The clinical presentation of both TS and PS included pain in the affected spine segment, radiating along the nerve roots, along with symptoms of body intoxication. Severe pain and immobility were observed in 18(36±0.68%) patients with TS and 13(7±0.69%) patients with PS. Both TS and PS patients had BCG vaccination scar, BCG vaccination and revaccination scars were determined in 30(40±0.57%) patients with TS and 20(40±0.69%) patients with PS.

Intoxication syndrome was expressed by fatigue, increased body temperature, decreased appetite. Laboratory tests revealed moderate anemia (TS-Hb 118±9.04 g/l, erythrocytes - 3.6±0.31*10^{12}/l; PS-Hb 118.3±15.4 g/l and erythrocytes - 3.6±0.5*10^{12}/l), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) procalcitonin (PCT) and fibrinogen (Fg) elevation: TS -CRP 65.3±50.7 mg/ml, ESR 30.5±18.4 mm/h, PCT 0.15±0.07 ng/ml and Fg 7.75±3.8 g/l; PS- CRP 117.3±107.9 mg/ml, ESR 39.4±21.7 mm/h, PCT 0.3±0.2 ng/ml, Fg 6.8±3.3 g/l. The leukocyte formula remained within the normal range in TS: leukocytes - 6.7±1.1*109, band cells - 1.3±0.9%, segmented cells - 64.2±5.1%, eosinophils - 1.6±0.8%, lymphocytes - 27.2±4.1%, monocytes - 5.5± 1.9%. In PS patients the leukocyte formula was also within the normal range: leukocytes - 8.3±2.9*109, band cells - 1.9± 1.4%, segmented cells - 62.5±3.1%, eosinophils - 2.2±1.3%, lymphocytes - 26.8±2.4%, monocytes - 6.5±1%. Toxic hepatitis with increased transaminase levels and liver enlargement on ultrasound was noted in 7 (9.3±0.34%) TS patients and 11 (22±0.59%) PS patients. Weight loss was observed in 10 (13.3±0.39%) patients with TS, while no weight loss was found in patients with PS.

MRI and CT features of TS were the thoracic spine involvement in 50.7±0.58% of cases, with 3 or more adjacent vertebrae affected and formation of kyphosis in 22.7±0.48%. Bone tissue destruction occurred in 90.7±0.34%, and total vertebral destruction was seen in 36±0.55% of cases. Osteoporosis of the paravertebral bone tissue was founded in 58.7±0.57%. Subligamentous spread to one, two, or three vertebrae was observed in 25.3±0.5%, and the intervertebral disc remains intact in 16% of cases. In patients with PS MRI and CT predominantly showed involvement of the lumbar spine in 39 (78±0.59%), with the intervertebral disc affected in all cases, no vertebral collapse, no involvement of the vertebral pedicles, no sequester formation and subligamentous abscess spreading to two or more vertebrae (Table 1).

Table 1. Frequency of occurrence, sensitivity, specificity and positive predictive value of MRI and CT signs of TS correlative to PS

VISUAL SIGN	TS, n=75	PS, n=50	Sensitivity	Specificity	Positive predictive value
Localization					
Cervical vertebrae	2(2,7±0,19%)	6(12±0,46%)	2,7%	89,1%	14,3%
Thoracic vertebrae	38(50,7±0,58%)	3(6±0,34%)	50,7%	89,2%	89,4%
Lumbar vertebrae	29(38,7±0,56%)	39(78±0,59%)	38,7%	43,5%	33,9%
Sacral vertebrae	7(9,3±0,33%)	2(4±0,28%)	9,3%	95,8%	66,7%
Prevalence of the process					
Lesion of 3 or more vertebrae	17(22,7±0,48%)	1(2±0,2%)	22,7%	97,5%	91,7%
Damage to the intervertebral disc and narrowing of the intervertebral space	63(83,9±6,6%)	50(100%)	83,9%	13,8%	45,7%
Damage to the endplates	66(84±0,42%)	33(66±0,67%)	84%	15,4%	57,1%
Destruction of the vertebral bodies	68(90,7±0,34%)	26(52±0,71%)	90,7%	16,1%	63,4%
Vertebral collapse (compression)	27(36±0,55%)	0	36%	100%	100%
Involvement of the vertebral pedicles	7(9,3±0,34%)	0	9,3%	100%	100%
Structure of bone tissue					
Unclear border of the lesion	44(58,7±0,57%)	7(14±0,49%)	58,7%	75%	80,6%
Clear border of the lesion	19(25,3±0,5%)	26(52±0,71%)	25,3%	58,7%	33,3%
Sclerosis of the surrounding bone tissue	2(2,7±0,19%)	13(26±0,62%)	2,7%	78,7%	13,3%
Sequesters	10%	0	58,7%	75%	80,6%
Abscesses					
Paravertebral abscesses	56(74,7±0,5%)	30(2,9±2,0%)	74,7%	30,2%	55,2%
Abscess spreads subligamentously to 2 or more vertebrae	19(25,3±0,5%)	0	25,3%	100%	100%

We analyzed P1NP bone formation marker (amino-terminal propeptide of type I procollagen, which is produced during the synthesis of type I collagen by osteoblasts) in 75(100%) patients with TS and 50(100%) patients with PS. The reference value for this marker in blood serum is <58.59 ng/ml. (Table 2).

Table 2. P1NP level in patients with TS and NS

Diagnosis	Age	P1NP, N<58,59 нг/мл
TS	Over 55	72,2±22,0 нг/мл
	Under 55	101,9±99,0 нг/мл
PS	Over 55	36,6±20,7 нг/мл
	Under 55	48,1±23,7 нг/мл

P1NP levels in patients with TS were higher than normal, while in patients with PS, they remained within the normal range. However, when bone destruction was visibly present, P1NP levels always exceeded the normal range, regardless of the diagnosis. We assessed the diagnostic significance of elevated P1NP for differentiating TS from nonspecific spondylitis, with a sensitivity of 84.2%, specificity of 62%, and a positive predictive value of 95.2%.

Active pulmonary tuberculosis was diagnosed in 10 (13.3 ± 0.39%) patients, active TB pleurisy in 5 (6.7 ± 0.28%), and signs of previous tuberculous lesions of the lungs in 27 (36 ± 0.55%) TS patients. Seven (14 ± 0.49%) PS patients presented with previous tuberculous lesions of the lungs.

QFT was assessed in all 75 (100%) patients with TS. A positive result was found in 63 (84±0.4%) patients, while 12 (16±0.4%) patients had a negative result. Patients with negative QFT results were also administered a Diaskintest and one (1,3±0.13%) patient showed a positive result. Tuberculous inflammation was histologically identified in the surgical specimen of 3 (4±0.23%) patients, confirming the diagnosis of TS. Bacteriological analysis revealed Mycobacterium tuberculosis in the surgical material of 9 (12±0.38%) remained QFT negative TS patients, with histological confirmation of tuberculous inflammation in 2 (2.7±0.19%) of them. Additionally, sensitive mycobacteria were found in 4 (5.3±0.26%) patients, while 3 (4±0.23%) cases showed resistance to rifampicin and isoniazid, and traces of mycobacteria were detected in 2 (2.7±0.19%) patients.

5. Discussion

Approximately 25% of the global population is infected with Mycobacterium tuberculosis. The risk of active tuberculosis development increases with greater immunodeficiency, which is caused by the growing population living with HIV (39.9 million people worldwide in 2023), diabetes (537 million adults in 2021 [15]), liver diseases (1.69 billion people in 2019 [9]), autoimmune diseases, and the use of corticosteroids.

The primary diagnostic methods for TS include MRI, CT, tuberculin skin tests, and IGRA tests. TS is most commonly differentiated from PS, which accounts for 1.5-2% of all osteomyelitis cases [17].

Ahmad N et al, 2020 determined overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of magnetic resonance imaging in diagnosing spinal tuberculosis, taking histopathology findings as gold standard was 92.13%, 84.48%, 90.11%, 87.50% and 89. 12% respectively [2].

In our patient population, highly suggestive visual signs of TS and their prevalence were as follows: thoracic spine involvement in 50.7%, involvement of more than two vertebrae in 22.7%, vertebral body collapse in 36%, involvement of the vertebral pedicles in 9.3%, unclear boundaries of the destruction cavity in 58.7%, sequesters in 10.6%, and subligamentous abscess spread to two or more vertebrae in 25.3%.

Bone tissue destruction is both a pathogenetic stage of TS and a frequent (over 90%) visual indicator of the condition. This destruction is associated with an increase in PINP levels in the blood during TS, following bone surgeries, and in cases of bone metastases. Ying M et al. (2023) showed the significance of bone-specific alkaline phosphatase, pro-collagen type I N-terminal pro-peptide (PINP), and pro-collagen type I C-terminal pro-peptide (PICP) markers as prognostic and predictive indicators of bone metastases in prostate cancer patients [16].

We have determined the diagnostic value of elevated P1NP for the differential diagnosis of TS and PS, sensitivity 84.2%, specificity 62%, positive predictive value 95.2%.

Hamada Y et al, 2022 in their systematic review and meta-analysis found, that when combining all studies on Diaskintest, C-Tb, and C-TST, the pooled sensitivity in TB infection was 76% (95%CI: 70–81%, 17 studies) in individuals with HIV-negative or unknown status and 63% (95%CI: 53–73%, 5 studies) in HIV-positive individuals. Two studies assessed test sensitivity of QFT 90% (95%CI: 79–95%) in TB infection. In four head-to-head studies including both adults and children with and without HIV, IGRA sensitivity was 72% (95%CI:63-79%) in TB infection. The pooled sensitivity across 6 studies on IGRA was 77% (95%CI: 66-85%) in TB infection [8]. However, due to possible latent tuberculosis infection and BCG vaccination, it is difficult to draw unambiguous conclusions regarding the specificity of tuberculin skin tests and IGRA tests.

In our study, among the 12 (16±0.4%) patients with a negative QFT result, tuberculous spondylitis was confirmed histologically in 3 (4±0.23%) patients, bacteriological confirmation was obtained in 7 (9.3±0.33%) patients, and both histological and bacteriological confirmation was obtained in 2 (2.7±0.19%) cases.

Based on the presented material, we proposed a point system of diagnostic criteria for TS (Table 3).

Table 3. Point system of diagnostic criteria for TS

1. Evaluation of imaging (X-ray, MSCT, MRI) signs, select one:	
Damage to the intervertebral disc, narrowing of the intervertebral space, inflammatory swelling of two adjacent vertebrae.	**46 points**
Damage of the endplates of two adjacent vertebrae, inflammatory edema, P1NP above 58.59 ng/ml – **57 points**. The specified changes in 3 or more vertebrae – **92 points.**	**57-92 points**
Vertebral body destruction, P1NP above 58.59 ng/ml, paravertebral infiltration – **63 points.** If the boundary of the bone destruction focus is unclear (osteoporosis) – **81 points.** The specified changes in 3 or more vertebrae – **92 points.** If the picture is supplemented by vertebral collapse (compression) – **100 points.**	**63-100 points**
Paravertebral abscess – **55 points.** If the abscess extends subligamentously to 2 or more vertebrae – **100 points.**	**55-100 points**
2. Evaluation of the nature of the disease	
The inflammatory nature of the disease is considered proven by a combination of **3 or more** of the following laboratory criteria. -Increased ESR in the blood -Leukocytosis -Shift in the leukocyte formula to the left -Lymphopenia -Increased fibrinogen -Increased procalcitonin -Increased CRP	**50 points**
3. Tuberculin diagnostics	
Positive tuberculin skin test	76 **points**
Positive IGRA test	**84 points**
4. Histologically proven tuberculous inflammation	**100 points**
5. Bacteriologically detected Mycobacterium tuberculosis	**100 points**
The diagnosis of tuberculous spondylitis is considered established at **146 points or more.**	

6. Conclusions

Both CT and MRI should be performed for diagnosing TS cases, because MRI is more sensitive for detection of bone and soft tissue edema, and CT shows bone structure. Early diagnosis of TS continues to pose a significant public health challenge and requires a comprehensive approach, relying on radiological assessments, immunological tests, as well as histological and bacteriological results.

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