Differentiated Approach to the Diagnosis and Treatment of Tuberculous Spondylitis in Adults

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Abstract- The purpose of this study is to generalize the results of a complex clinical-laboratory, radiological and immunological study of patients with spinal tuberculosis. A comprehensive examination analysis was carried out in 192 patients with tuberculous spondylitis who were in the department of surgery for osteoarticular tuberculosis of the Republican Specialized Scientific and Practical Medical Center of Tuberculosis and Pulmonology in Tashkent, Uzbekistan. Severe degrees of spinal disorders were found in 48.7% of patients. Magnetic resonance imaging (MRI) and multi-slice spiral computed tomography (MSCT) allow establishing the stage and activity of a specific process in the spine, as well as complications. Spinal column instability was detected in 143 (74.5%) patients, paravertebral abscesses in 116 (60.4%) patients, and epidural abscesses in 75 (39.0%) patients. Changes in immunological parameters in patients with spinal tuberculosis were associated both with impaired regulation of immunogenetic and with the direct influence of the immune system at various stages of the process. The detection of certain patterns of immune system disorders in patients with tuberculous lesions of the spine allowed us to make a differentiated approach to their treatment in order to increase the effectiveness of the treatment. It can be concluded that at present, tuberculosis of bones and joints, especially the spine, is detected in an advanced stage in 50-80% of cases and has a widespread and complicated character with profound anatomical and functional changes and the presence of severe spinal disorders in 48.7% patients in Uzbekistan. Regarding spondylitis, it is immensely important to make an accurate diagnosis based on the clinical presentations, laboratory, radiological and immunological findings and by periodic assessment of the response to treatment, which is essential in atypical cases.

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Introduction

Tuberculosis spondylitis or spinal tuberculosis has been known since ancient times. Hippocrates and Galen also mentioned this disease in their medical investigations. In 1779, the first detailed description of its main symptoms (hump and related paralysis) was given by the English surgeon Persivewell Pott, who consequently named this disease in the English literature as “Pott`s disease” (1).

Tuberculous spondylitis is one of the most serious chronic infectious diseases caused by *Mycobacterium tuberculosis* affecting the vertebral bodies, spinal cord, and surrounding organs (2,3). In addition, it is characterized by the formation of specific granuloma and the progressive destruction of the bone, leading to severe organic and functional disorders of the affected skeleton. It also occurs much more often than it is registered. For instance, only a smaller part of the patients suffering from tuberculous spondylitis is actively and timely detected (4,5), and therefore some patients do not receive timely and correct treatment (6,7,8).

In recent years, tuberculosis spondylitis or spinal tuberculosis has shown a considerable resurgence in not only developing countries, but also in developed ones,

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particularly among the immunosuppressed population, mainly as a consequence of higher human immunodeficiency virus (HIV) infection and immigration rates (9). This disease has become a serious challenge to the global community. For a few decades, an inauspicious upward trend in the number of multidrug-resistant tuberculosis strains is observed in developing countries. Due to these reasons, currently, the disease continues to exist as a critical global public health menace (10). The diagnosis of tuberculous spondylitis remains a clinical challenge despite all technological advances since it depends on a high grade of clinical suspicion. In spite of the low reported mortality of tuberculous spondylitis, this condition is still associated with substantial clinical morbidity. Particularly, considerable delay in diagnosis may lead to irreversible neurological complications and severe skeletal deformities (11). Moreover, the slow development of a specific process in the spine, unclear symptoms, and the long course of tuberculosis gradually turn the patient into a severely disabled person. A number of such patients are accumulating, their treatment and maintenance require material costs, and hence, it all turns into a medical and social problem (8,12). At the same time, thanks to the achievements of modern medicine (mainly surgery) in the Republic of Uzbekistan, all localizations and forms of tuberculous spondylitis are treatable (13,14).

The spinal tuberculosis diagnosis, as a rule, is based on a comprehensive assessment of clinical manifestations, such as data from laboratory analyses and the results from radiological studies (7,15-19). However, even with the presence of high-tech diagnostic methods, tuberculous spondylitis is still detected in 40% of cases in the later stages, and common and complicated forms are found in 70% of adult patients (8,20-22).

According to the number of researchers (6,7), the clinical and radiological data similarity of these borderline diseases leads to the fact that the majority of patients with nonspecific spine osteomyelitis are sent for treatment to specialized hospitals with an erroneous preliminary diagnosis of tuberculous spondylitis. At the same time, the authors note that the accumulated experience in the treatment of tuberculous spondylitis in TB hospitals can be used in the treatment of patients with nonspecific inflammatory diseases of the spine (23,24).

The purpose of this study is to generalize the results of a complex clinical-laboratory, radiological and immunological study of patients with spinal tuberculosis.

Materials and Methods

A comprehensive examination analysis was carried out in 192 patients with tuberculous spondylitis who were in the department of surgery for osteoarticular tuberculosis of the Republican Specialized Scientific and Practical Medical Center of Tuberculosis and Pulmonology in Tashkent, Uzbekistan. The anamnesis, clinical and laboratory data (general analysis of blood, urine, biochemical research, and a blood coagulogram), ECG, HPF, ultrasound of the abdominal cavity, pelvis, and retroperitoneal space, as well as the pleural cavity, were studied. Neurological status was assessed using the Frankel scale.

The radiological examination was carried out using X-ray in the sagittal and frontal projections and MRI of the affected segment. CT and MRI were performed according to indications for the differential diagnosis of the pathological process. The study was conducted on MRJ SYGNA HD/e (General Electric USA) apparatus with a capacity of 1.5 Tesla and MSCT (32 slices). MSCT and MRI examination were studied in sagittal, frontal, and axial projections. The thickness of the tomographic section of MSCT was from 2 to 5 mm. Sputum, postoperative material, fistula contents, pus, punctate, pleural fluid were subjected to bacteriological examination. The methods of bacteriological research were performed using smear microscopy, Gene-Xpert/Rif molecular genetic analysis, HAIN test, culture study on solid Levenshtein-Jensen medium, followed by automated incubation and growing of mycobacterial cultures on MGYT-960 liquid medium using BACTEC-MGYT- apparatus 960, as well as by determining the sensitivity of *Mycobacterium tuberculosis* to antibiotics. The immune status was studied in 100 patients using indicators of cellular and humoral immunity. Such study was based on the determination of the percentage of lymphocytes, the number of T- and B-lymphocytes, subpopulation of T-lymphocytes-T-helpers and T-suppressors. The phenotype of immunocompetent cells was determined using monoclonal antibodies CD3, CD4, CD8, CD25, and CD95 (manufactured by Sorbent-ZTD) according to the Aguiar *et al*., (25) method. The level of serum immunoglobulins in the secrets composition was determined by the method of radiological immunodiffusion according to the Lighaam and Rispens (26) and Mancini G. *et al*., (27) method using standard monospecific antisera, which was received from NI Mechnikov Scientific Research

Institute of Microbiology, Moscow.

Results

The age of patients ranged from 20 to 70-year-old (average age-42-year-old): 102 men (53.1%) and 90 women (46.9%). Tuberculous spondylitis, detected for the first time, amounted to 144 (75.0%) patients and was previously registered in the dispensary-48 (25.0%). By localization: the lumbar spine was affected in 70 (36.5%) patients, the lumbosacral in 40 (20.8%), the lumbar in 40 (20.8%), the thoracic in 22 (11.5%), cervicothoracic in 10 (5.2%) and cervical in 10 (5.2%) patients.

A relatively frequent lesion of the lumbar, lumbar-sacral, and thoracolumbar spine was noted, which can be explained either by a heavy load or trauma of a different nature (trigger): acute or chronic associated with a professional or anatomical-functional structure, massive bleeding, etc.

Injuries of a different nature, and orthopedic changes (scoliosis of varying degrees), and chronic concomitant diseases are triggers in the pathogenesis of tuberculosis of bones and joints with a premorbid background. Concomitant diseases were found in 144 (75.0%) patients. A cardiovascular system disorders were found in 89 (46.4%) patients, anemia of a different nature in 69 (35.9%), the hepatobiliary system in 29 (15.1%), diseases of the urinary system and genitals in 13 (6.7%), and diabetes mellitus in 13 (6.8%) patients.

A generalized form of spinal tuberculosis with lung damage was detected in 24 (12.5%) patients. Mycobacterium tuberculosis was revealed in the sputum of these 11 (45.8%) patients.

The inflammatory process was accompanied by severe intoxication syndrome: an increase in body temperature (before the febrile illness) was observed in 85 (44.3%) patients, weakness and sweating in 53 (27.6%), loss of appetite in 125 (65.1%), and weight loss more than 10 kg in 104 (54.2%) patients.

The most formidable complication of tuberculous spondylitis is spinal cord compression, leading to paresis, paralysis of the extremities, impaired function of the pelvic organs, abdominal cavity, etc. Neurological complications of a different nature were revealed in 154 (80.2%) patients.

As can be seen from Table 1, a deep neurological disorder of type A was found in 2 (1.0%) patients with anesthesia and plegia below the level of the lesion. B type (incomplete sensitivity violation below the level of the lesion and lack of movement) was found in 3 (1.6%) patients. Type C (incomplete sensitivity violation, weak movements, but muscle strength is insufficient for walking) was found in 10 (5.2%) patients. Type D (incomplete sensitivity violation below the lesion level, there are movements and muscle strength sufficient for walking, but with extraneous help) was found in 60 (31.3%) patients. Type E was found in 79 (41.1%) patients without impaired sensitivity and movements below the level of damage but with the severe radicular syndrome.

Table 1. The degree of neurological complications in the examined patients

Degree of impairment	A	B	C	D	E
Number of patients N=154	2 (1.0%)	3 (1.6%)	10 (5.2%)	60 (31.3%)	79 (41.1%)

The more disturbing fact was that in the preoperative period, despite adequate antibiotic therapy during the orthopedic regimen, exacerbated neurological status in the form of weakness in the lower extremities, impaired urination, and a tendency to constipation were observed in 3 (5.0%) patients of type D and 8 (10.1%) patients of type E.

Histological and/or bacteriological confirmation of the diagnosis “tuberculosis” was obtained in 75 patients with spondylitis.

Examination of 64 (33.3%) patients showed kyphotic deformity, spinal column instability in 143 (74.5%) patients, paravetebral abscesses in 116 (60.4%) patients, and epidural abscesses in 75 (39.0%) patients.

According to MRI data, a peak of the spondylitis phase was noted in 38 (50.7%) patients with a decrease in the signal from the vertebral body remainder, destroyed by the closure plate, paravertebral soft tissue infiltration in T1 mode, an increased signal from the remainder of the vertebra and from the disk involved in the process in T2 mode, and also a high signal from the contact destruction cavity (homogeneous or heterogeneous). Radiologically, this was manifested by the transition of the destructive process to two or more vertebral bodies, parafibular osteoporosis in the form of a decrease in the optical density of bone tissue, and a blurred border around the destruction site. Clinically, this was manifested against the background of intoxication syndrome by severe radicular pain, paravertebral abscesses, and spinal disorders. Spondylitis was diagnosed in 19 (25.4%) patients against a background of the pain-radicular syndrome. 15 (20.0%) patients with detected tuberculous spondylitis

were preceded by the development of spinal disorders, and 4 (5.3%) patients had the formation and opening of abscesses. MRT image of one of the selected patients is given in Figure 1 for reference.

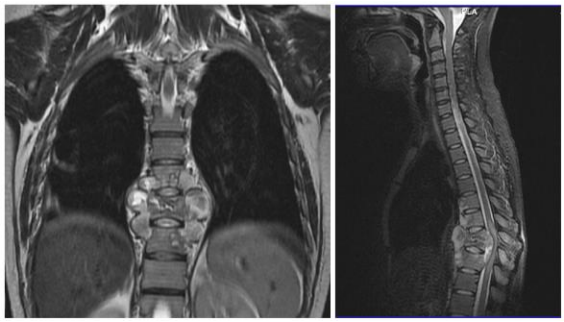

Figure 1. Tuberculous spondylitis Th 6-7-8-9-10, spondylitis phase: MRI of the thoracic spine, coronary and sagittal projection (focal and contact destruction in Th 6-7-8-9-10 bodies with the destruction of Th 8-9 bodies and compression fracture; multi-chamber abscesses with an inhomogeneous signal with end plates destruction in the epidural and paravertebral regions)

A decreased spondylitis phase was found in 37 (49.3%) patients on the basis of clinical and radiological data, which was manifested by an inhomogeneous low signal from the destructive contact cavity and a reduced signal from the body remainder, as well as by abscesses formation in the T1 mode, and frequent decrease in the inhomogeneous signal from the destructive cavity and an unchanged or increased signal from the vertebral body in T2 mode. In addition, the spondylitis phase was manifested by the clarity of the boundary of the destruction center on radiographs. However, the bone tissue around the destruction site remained porous or acquired a large-loop pattern (see Figure 2 for the reference).

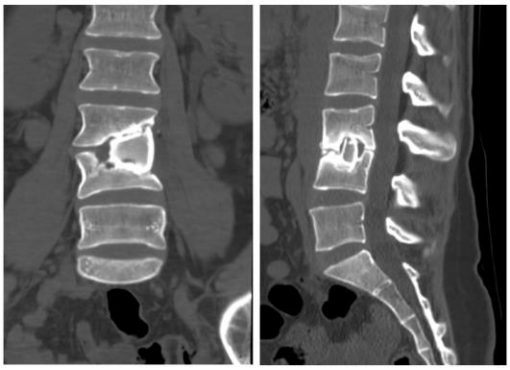

Figure 2. Tuberculous spondylitis L3-4: CT scan of the lumbar spine, coronary and sagittal projection (a block was formed from the remnants of L3-4 bodies, without fresh destructive changes; soft tissues are densified in the paravertebral region, there are no abscesses)

Clinically, intoxication syndrome was less intense in these patients, and pains in the spine came to the fore during stress due to instability of the spine, and tuberculous spondylitis was detected after MSCT in 6 (8.0%) cases due to soreness and fatigue of the lower back muscles.

Discussion

In clinical practice, as a rule, a conclusion about the state of immunity in a particular patient is given on the basis of a study connected with the main populations of immunocompetent cells (CD3-T-lymphocytes, CD4-T-helpers, CD8-T-suppressors, and CD20-B lymphocytes, NK-cells, etc.). In addition, the immunoregulatory index (IRI) is taken into an account-the ratio of SD4/SD8. According to this indicator, it can be judged in which of the two immunoregulatory populations (T-helpers and T-suppressors) more pronounced changes occur. However, the above indicators reflect only quantitative indicators of T- and B-immunity.

The state of immunological status was studied in 45 patients with spinal tuberculosis and in 20 healthy people who made up the control group.

As can be seen from Table 2, the presence of leukocytosis and lymphocytosis in patients with spinal tuberculosis in the acute period confirms the development of the inflammatory process in the body. The interaction of T- and B-class lymphocytes and their subpopulations is the main component in the regulation of the immune system. According to Table 2, it is noted that the pathological process in tuberculosis of the spine is accompanied by compensatory stimulation of the immune system's cellular mechanisms. Hence, the absolute number of T-lymphocytes and their percentage significantly increased in the main group.

At the same time, there was a significant increase in T-helpers and a decrease in T-suppressors. IRI increment in spinal tuberculosis indicates the development of autoimmune processes in the body, which led to a chronic process.

When assessing changes in the humoral immunity in the examined patients, a significant increase in B lymphocytes was revealed compared with the control (17.3±0.17% versus 13.2±0.42%). A similar pattern is observed with respect to immunoglobulin a (5.89±0.07 g/l against 2.93±0.09 g/l) and G immunoglobulin (19.4±0.36 g/l against 15.98±0.51 g/l).

Infection, medication, and changes in the protein composition of the plasma could be the reason for the formation of immune complexes. Structural changes in

the vascular wall and collagen synthesis violation lead to contact stimulation of platelets and provokes micro-thrombosis.

Table 2. Indicators of cellular immunity in the examined patients

Indicators	Control group (n=20)	Main group (n=55)	*P*
Leukocytes *10^9/l	4.19±0.21	8.83±0.43	<0.001
Lymphocytes *10^9/l	1.31±0.11	2.89±0.7	<0.01
Lymphocytes %	31.19±1.36	40.41±5.31	>0.05
T- lymphocytes *10^9/l	0.75±0.09	1.33±0.05	<0.001
T – lymphocytes %	57.87±5.78	66.29±8.33	<0.05
SD4 + (T - helpers) *10^9/l	0.25±0.09	0.31±0.02	<0.05
SD4 (T - helpers), %	34.89±2.67	51.14±3.98	<0.001
SD8 (T - suppressors), %	27.3±0.41	23.18±0.91	<0.05
Immunoreactive insulin (IRI)	1.32±0.22	2.56±0.03	<0.001

Consequently, changes in immunological parameters in patients with spinal tuberculosis are associated both with impaired regulation of immunogenetic and with the direct influence of the immune system. Nevertheless, questions of the functional state of the immune system in this category of patients whose immune status and antibody titers in a specific process remain insufficiently studied. The study of these issues is of both scientific and practical interest, and the ultimate goal is not only to detect certain patterns of the immune system development in this group of patients but also a differentiated approach to their treatment in terms of increasing efficiency.

1. At present, tuberculosis of bones and joints, especially the spine, is detected in an advanced stage in 50-80% of cases and has a widespread and complicated character with profound anatomical and functional changes and the presence of severe spinal disorders in 48.7% of patients in Uzbekistan.
2. MRI and MSCT allow establishing the stage and activity of a specific process in the spine, as well as complications. Spinal column instability was detected in 143 (74.5%) patients, paravertebral abscesses in 116 (60.4%) patients, and epidural abscesses in 75 (39.0%) patients.
3. Changes in immunological parameters in patients with spinal tuberculosis were associated both with impaired regulation of immunogenetic and with the direct influence of the immune system at various stages of the process. The detection of certain patterns of immune system disorders in patients with tuberculous lesions of the spine allowed us to make a differentiated approach to their treatment in order to increase the effectiveness of the treatment.
4. It is immensely important to make an accurate diagnosis based on the clinical presentations, laboratory, radiological and immunological findings and by periodic assessment of the response to treatment, which is essential in atypical cases.

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