

Extrapulmonary tuberculosis, clinical presentation and outcome

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ABSTRACT

Objective: To identify patterns, features, and outcome of extrapulmonary tuberculosis in a tertiary care setting.

Methods: A retrospective case-series was carried out of all cases diagnosed and treated as extrapulmonary tuberculosis during 1991 through to 2000 at King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Kingdom of Saudi Arabia. Demographic, clinical, laboratory, and outcome data were abstracted from medical records.

Results: Over a 10-year period, 394 cases of extrapulmonary tuberculosis were diagnosed and treated at KFSH&RC. Isolated extrapulmonary tuberculosis was identified in 339 (86%) patients, 55 cases (14%) had both pulmonary and extrapulmonary tuberculosis. Mean age

was 45-years, and 188 patients (47%) had co-morbidities, most commonly diabetes mellitus in 14.2% of patients. Laboratory confirmation of extrapulmonary tuberculosis was available on 386 patients. The most frequent site involvement was lymphadenopathy in 41% of the time. Chest x-ray was normal in 75% of patients. Among 298 patients with follow up data, 10 (3.4%) had documented relapse and 50 (16%) died. Death was related to tuberculosis in 24 (48%) patients.

Conclusion: A high level of clinical suspicion is essential for early diagnosis and treatment of extrapulmonary tuberculosis to reduce the significant morbidity and mortality.

Saudi Med J 2004; Vol. 25 (7): 881-885

In spite of major improvement, tuberculosis remains an endemic disease in the Kingdom of Saudi Arabia (KSA).¹ Extrapulmonary tuberculosis (EPT) has the reverse epidemiological trend of pulmonary tuberculosis. Over the last several years, reported extrapulmonary tuberculosis was increasing in absolute numbers and proportion of all reported tuberculosis cases.² Although this trend may be related to several factors including better health services and reporting, the mere proportion of all tuberculosis cases that have extrapulmonary involvement is significant. The associated delay in diagnosis of extrapulmonary tuberculosis results in increased morbidities and mortalities. The manifestations of extrapulmonary tuberculosis are

so protean that diagnosis and identification is often delayed. The 2 large series of extrapulmonary tuberculosis reported from KSA have been published 20-years ago.^{3,4} The various patterns of extrapulmonary tuberculosis and difficulties in diagnosis and outcome have not been visited since then. There have been several reports addressing a specific form of extrapulmonary tuberculosis but not the various patterns and their relative proportions.⁵⁻¹⁰ As the health care services improve, immune suppression conditions increase, and diabetes prevalence continues to increase,¹¹ more of these extrapulmonary tuberculosis cases will be presented to health care providers. Awareness and clinical suspicion of extrapulmonary tuberculosis

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Received 29th October 2003. Accepted for publication in final form 21st February 2004.

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will undoubtedly result in early recognition, diagnosis and treatment. In this study we present the various patterns, features and outcome of extrapulmonary tuberculosis diagnosed and treated at KFSH&RC.

Methods. Cases of tuberculosis were identified from the databases of infectious diseases service, infection control, and the microbiology laboratory. Demographic data, clinical and laboratory findings, and outcome were abstracted from medical records. Cases of extrapulmonary tuberculosis were defined for the purpose of this report as any case diagnosed and treated for tuberculosis where organs other than the lungs were involved by *Mycobacterium tuberculosis* (*M.tuberculosis*). If lungs were actively involved as evidenced clinically, radiologically or microbiologically, the condition was considered as mixed and grouped as such differently. Isolated pulmonary involvement was excluded from this study. The study period is from 1991 till the end of 2000 and the setting was KFSH&RC. Data concerning clinical presentation and initial working diagnosis, radiological and laboratory findings were collected on all patients from initial and follow up visits. Relapse was defined as recurrence of symptoms and laboratory confirmation or favorable response to antituberculosis therapy after completing the first course. Mortality data were collected and assigned as tuberculosis-related or unrelated as judged by a single reviewing investigator.

Data collection and analysis. Epi Info Version 6.04 (Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America (USA), and World Health Organization, Geneva, Switzerland) was used for data entry. Statistical analysis was performed using Statistica Software package Version 5.0 (StatSoft, Tulsa, Oklahoma, USA). The Student's t test was used to calculate continuous variables, and the Chi-square or Fisher's exact test was used for proportions. All reported *P* values are 2-tailed and a value of <0.05 was considered significant.

Results. Between 1991 and 2000, there were 535 cases of tuberculosis diagnosed at KFSH&RC. Isolated pulmonary tuberculosis was diagnosed in 141 cases (26%), extrapulmonary tuberculosis in 339 cases (63%), and both pulmonary and extrapulmonary in 55 cases (10.3%). The basic demographic data for patients with extrapulmonary tuberculosis are presented in **Table 1**. Extrapulmonary tuberculosis was diagnosed and treatment offered for all 394 patients. Only 8 (2%) patients had the diagnosis and treatment based on clinical findings alone; 386 patients had tissue processed for laboratory confirmation of their

Table 1 - Basic demographics of extrapulmonary tuberculosis and mixed involvement.

| Criteria | Extrapulmonary 339 patients n (%) | Mixed involvement 55 patients n (%) |
|--|---|---|
| Mean age, y (years) | 45 | 44.5 |
| Female to male ratio | 1.15 | 0.72 |
| Origin | | |
| Central region | 139 (41) | 24 (43) |
| Western region | 41 (12) | 11 (20) |
| Eastern region | 28 (8) | 1 (2) |
| Southern region | 58 (17) | 5 (9) |
| Northern region | 30 (8) | 6 (10) |
| Non-Saudi | 19 (5) | 2 (3) |
| Not known | 24 (7) | 6 (10) |
| Proportion with co morbidities | 156 (46) | 32 (58) |
| Mean duration of symptoms before diagnosis, m | 7 | 5.7 |

Table 2 - Laboratory findings among 394 patients with extrapulmonary tuberculosis.

| Findings | No culture | Positive culture | Negative culture | Totals |
|--------------------|------------|---------------------|---------------------|------------|
| No pathology | 8 | 65 | 2 | 75 |
| Positive pathology | 18 | 211 | 48 | 277 |
| Negative pathology | 1 | 32 | 9 | 42 |
| Total | 27 | 308 | 59 | 394 |

syndrome. Pathology findings were available for 319 (80%) patients, they were consistent with tuberculosis in 277 (86%) patients, while 42 patients had findings not consistent with tuberculosis, 32 patients of them had positive cultures for *M. tuberculosis*. Tissue specimens were processed for acid-fast bacilli culture from 367 (93%) patients. Culture results were positive from 308 (83%) and negative in 59 (16%) patients, 48 patients of them had pathology findings consistent with tuberculosis. There were 9 patients (2%) who had specimens processed for histopathology and culture but could not be confirmed. However, response to antituberculosis therapy was indicative of tuberculosis in these patients. **Table 2** summarizes the laboratory findings for the 394 patients with extrapulmonary tuberculosis. Mean duration of symptoms before diagnosis of extrapulmonary tuberculosis was 7-months. Mantoux skin test was performed for 129 patients, 30 of them had measurement less than 5 mm after 48-hours and

Table 3 - Distribution of tuberculosis involvement in extrapulmonary tuberculosis.

| Distribution | Extrapulmonary n (%) | Pulmonary and extrapulmonary n (%) | Total n (%) |
|--|-------------------------|---------------------------------------|-----------------|
| Lymphadenopathy | 204 (41) | 42 (39) | 246 (41) |
| Vertebral | 45 (9.1) | 2 (1.9) | 47 (7.8) |
| Abscess | 28 (5.7) | 4 (3.7) | 32 (5.3) |
| Peritoneal | 26 (5.3) | 6 (5.6) | 32 (5.3) |
| Brain tuberculoma | 27 (5.5) | 2 (1.9) | 29 (4.8) |
| Bone and joints | 24 (4.9) | 2 (1.9) | 26 (4.3) |
| Paravertebral and psoas abscess | 22 (4.5) | 2 (1.9) | 24 (4) |
| Bone marrow | 11 (2.2) | 11 (10) | 22 (3.7) |
| Meningitis | 13 (2.6) | 8 (7.4) | 21 (3.5) |
| Miliary | 11 (2.2) | 10 (9.3) | 21 (3.5) |
| Urogenital/scrotal | 13 (2.6) | 3 (2.8) | 16 (2.7) |
| Pleural | 11 (2.2) | 3 (2.8) | 14 (2.3) |
| Hepatic | 8 (1.6) | 5 (4.6) | 13 (2.2) |
| Intestinal | 7 (1.4) | 1 (0.9) | 8 (1.3) |
| Others | 43 (8.7) | 7 (6.5) | 50 (8.3) |
| Some patients had more than one site involvement; hence the total number of involvements is larger than the 394 patients with extrapulmonary disease | | | |

were considered negative. Positive Mantoux of 10 mm or more was noted in 99 patients with a mean induration measurement of 19 mm. There were 43 patients with Mantoux reading between 10 and 15 mm, 56 patients had readings more than 15 mm. Out of 339 patients with isolated extrapulmonary tuberculosis, chest radiography was normal in 253 (75%) patients, and 18 (5%) patients had chest radiography findings consistent with old inactive pulmonary tuberculosis. The rest of patients had abnormal chest x-ray but not related to tuberculosis. When patients were referred, neoplasm was the initial working diagnosis in 152 patients (38%), while an infectious process was the working clinical diagnosis in 164 patients (41%). The rest (19%) were thought to have other conditions (such as inflammatory, degenerative, for example). Lymphadenopathy was the most frequent site involvement of extrapulmonary tuberculosis noted in 246 out of 601 involvements (41% of the time), more than half of them in the cervical region. Vertebral tuberculosis was the second most frequent involvement noted in 47 patients. **Table 3** outlines the various site involvements for the 394 patients with extrapulmonary tuberculosis. Other rare and infrequent sites include skin, parotid glands, spleen,

stomach, mastoid process, finger, and endometrium. Co-morbidities were found in 188 (48%) patients. The most frequent co-morbidity was diabetes mellitus noted in 56 (14%) patients, followed by neoplasia or immunosuppression in 48 patients (12%) each. Chronic use of steroids was noted in 35 (8%) patients. Human immunodeficiency virus test results were available for 162 patients, 9 of them were positive and 153 were negative. Follow up and care were transferred to other facilities for 39 (9%) patients, and 55 (13%) patients were lost to follow up. Follow up data were available on 298 patients beyond treatment completion. Relapse was documented in 10 (3.4%) patients. Fifty (16%) patients died, 24 (48%) of them were related to tuberculosis while 26 (52%) were not related to tuberculosis.

Discussion. Extrapulmonary tuberculosis constitutes a significant fraction of tuberculosis impact on health and resources. Depending on population, extrapulmonary tuberculosis represents a variable proportion of all reported tuberculosis.¹²⁻¹⁴ In KSA, 27% of reported tuberculosis in 1998 had extrapulmonary involvement.¹⁵ Our institute has been managing more extrapulmonary tuberculosis

than pulmonary tuberculosis since its early days.^{3,16} This is mostly related to the referral patterns and our patient population. As a tertiary care facility, undiagnosed cases, cases suspected to have neoplasm, and patients requiring certain diagnostic procedures are referred more often than cases of pulmonary tuberculosis. Our institute is serving a large population of patients with immunocompromised conditions either genetically or related to chronic medical conditions, transplantation, cytotoxic chemotherapy, or HIV infection. Such immunocompromised patients are at a higher risk for extrapulmonary tuberculosis. Estimating the exact proportion of tuberculosis in the community with extrapulmonary tuberculosis is difficult. Difficulties are attributed to diagnosis and reporting. However, using the same reporting process, patterns are more reliable. These have been clearly on the rise recently.² The impact of the HIV epidemic is evident in many communities.^{14,17,18} The distribution of various forms of extrapulmonary tuberculosis is institute-dependent as of referral patterns. In KSA, tuberculous lymphadenopathy was the most frequent form in Jeddah, KSA, comprising 54% of extrapulmonary cases.⁴ It was 22% of the cases from Riyadh around the same time in the early 80's.³ In our series, it was the most frequent form noted in 41% of the involvements. This is essential to keep in mind as lymphoma remains an important differential in prolonged lymphadenopathy. In Aseer, the main reason for sampling an enlarged lymph node was to rule out lymphoma.⁸ Cervical involvement was noted in more than 55% of our patients with tuberculous lymphadenitis, close to other reports.^{8,19} Central nervous system disease was the most frequent in our hospital in 1982, up to 36% including vertebral involvement.³ It is still high, ranking second; 16% of all involvements. This disproportionate high rate of central nervous system tuberculosis is most likely related to referral of cases with brain lesions or seizures. Diagnosing extrapulmonary tuberculosis is often delayed. In this series, the average duration of symptoms before diagnosis was 7-months. When pulmonary tuberculosis was also part of the disease, extrapulmonary tuberculosis was diagnosed more rapidly. This may have resulted from several factors. Clinicians may not be suspicious of tuberculosis when it involves organs other than the lungs, work-up may not be available at local health facilities and patients may need to satisfy certain referral requirements before they are evaluated for extrapulmonary tuberculosis. Chest radiology is not consistent with tuberculosis in 75% of patients with isolated extrapulmonary disease. Mantoux skin test if requested may not be positive. Therefore, diagnosis relies heavily on tissue specimen processed for acid-fast bacilli culture and histopathology findings suggestive of tuberculosis.

As a referral center, almost all patient had tissue for laboratory confirmation. Out of 394 patients, only 17 (4%) of patients had no laboratory confirmation, half of them had no specimens sent for confirmation. These patients were considered to have tuberculosis based on favorable response to antituberculosis therapy. Outcome of extrapulmonary tuberculosis has not been reported from KSA before. Complications of some forms of extrapulmonary tuberculosis were reported before on spinal compression; for example.³ Confirmed relapse has not been reported among extrapulmonary tuberculosis. A relapse rate of 3.4% is relatively low. For mortality, we are not aware of any mortality data related to extrapulmonary tuberculosis from our country. The high rate of death (16.7%) among our patient population is related to the high proportion of patients with severe co-morbid illnesses. Tuberculosis related death of 48% is considerably high. It indicates the significant impact of extrapulmonary tuberculosis in severely ill patients. This clearly speaks for the need to identify and diagnose these patients early.

In conclusion, extrapulmonary tuberculosis constitutes a significant proportion of tuberculosis. It requires special clinical alertness to recognize the condition. The delay in identification and treatment results in significant morbidity and mortality. As clinicians have to be aware of the potential of extrapulmonary involvement, health care facilities have to be prepared with the required expertise and resources for confirmation.

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