Osteoarticular tuberculosis in a developed country

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Summary
Objectives: To evaluate the clinical and diagnostic features of osteoarticular tuberculosis (OT) from a series of cases seen over 30 years in a large university hospital in Naples, Italy.
Methods: We reviewed the files of all patients admitted to our department from 1975 to 2004 with a diagnosis of osteoarticular tuberculosis.
Results: We identified 136 patients with 140 osteoarticular tuberculosis lesions. Fifty-three cases were diagnosed from 1975 to 1984, 36 cases from 1985 to 1994, and 47 cases from 1995 to 2004. Eleven patients (8%) were from high-incidence areas outside of Italy. The mean delay until diagnosis was 216.6 days. Pain, low-grade fever, and loss of weight were the most common presenting symptoms. Neurological involvement was present in 11 cases out of 79 spinal lesions (13.9%). Serological methods were used to study antimycobacterial antibodies using enzyme-linked immunosorbent assays (ELISA-TB test) in 59 patients (42.1%). Positive results on this test were obtained in 43 patients (72.9%). ELISA-TB test was the only diagnostic test associated with a shorter diagnostic delay in a model of multivariate regression analysis ($p < 0.001$). Tc-99m MDP bone scans were obtained from 83 patients with 84 lesions and increased uptake in the affected area was noted in 72 lesions (85.7%). Histological and microbiological examinations were positive in 97 (69.3%) and 57 (40.7%) lesions, respectively. In 43 (30.7%) lesions, we could not definitively confirm the diagnosis. In these cases chemotherapy was nevertheless initiated.
Conclusions: Thorough and even invasive diagnostic work-up is mandatory for the proper and timely management of patients with OT. Tc-99m MDP bone scanning and ELISA-TB test are useful diagnostic tools. We always used microbiological testing and histological examination to confirm the diagnosis of OT, but empirical antituberculosis treatment was nevertheless initiated in the patients with high clinical suspicion in order to limit the potentially permanent destruction of affected skeletal segments.

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Introduction

Approximately 30 million people are currently affected by tuberculosis worldwide and 1–3% of them have skeletal involvement. In the late eighties and early nineties, there was an increase in the incidence of osteoarticular tuberculosis (OT) reported in Western countries. The main reasons for this epidemiological trend include an increase in immigration from regions in which tuberculosis is endemic, the increasing number of people with suppression of the immune system, ageing of the population, and development of drug-resistant strains of Mycobacterium tuberculosis. Naples, the largest metropolitan area in southern Italy with nearly 3,000,000 inhabitants, is the chief town of Campania, the most populated southern region of Italy. Among the Italian cities, Naples has the highest population density and also the immigration rate is relatively high. There is a lack of epidemiological and clinical data on OT in southern Italy and Naples area. This paper discusses the epidemiological, clinical and diagnostic features of OT from a series of cases seen over 30 years in a large university hospital in Naples, Italy.

Patients and methods

The teaching hospital of University Federico II of Naples, built on a site of 40,000 square metres (40 ha), consists of 19 buildings, each forming one or more departments, and is endowed with 1000 beds. The hospital is the largest medical facility without emergency ward in the area and it receives most patients with elective conditions in the uptake area; it provides secondary and tertiary cares to patients with diverse socioeconomic, occupational, and anthropometric characteristics. From 1997 to 2003 the Federico II University Hospital ranked first and second, respectively, for number of DH (35,577/year) and ordinary (45,255/year) discharges among Campania hospitals. Thus, we assume that our patients constitute a reliable sample of the entire population in the uptake area. We reviewed the files of all patients admitted between 1975 and 2004 to the Department of Orthopaedic Surgery of Federico II University Hospital with a diagnosis of osteoarticular tuberculosis. We analysed the demographic data for each patient, including age, gender and provenience, as well as medical history before, during and after admission to the hospital. All patients underwent the same diagnostic protocol, which included a physical examination, routine laboratory examinations, plain radiographs, a Mantoux skin test, computed tomography (CT) or magnetic resonance imaging (MRI), and a biopsy for histological and microbiological workups. The severity of the neurological deficits in patients with spinal cord involvement was retrospectively classified according to Tuli. Following this method, in Stage I there is clumsiness of gait and signs of upper motor neuron lesion, in Stage II motor weakness and signs of upper motor neuron lesion with preservation of walking ability, in Stage III the patient is bedridden due to severe motor weakness and has sensory loss of less than 50%, in Stage IV the patient is paraplegic with sensory loss of more than 50% and/or bladder or bowel involvement. Atypical spinal tuberculosis was diagnosed following the method of Pande and Babhulkar. Since 1996, all patients’ blood has been routinely tested for the hepatitis C virus (HCV). Since 1990 all patients with a suspicion of tuberculosis were tested for human immunodeficiency virus (HIV). Since 1992, we have used serological methods to study IgG and IgA antimycobacterial antibodies using enzyme-linked immunosorbent assays (ELISA-TB test) in 59 patients who also were our research subjects (42.1%). The A60 antigen, the main thermo-stable component of purified protein derivative, was used for this test. Cut-off values had been previously assessed using receiver operating characteristic (ROC) curves. To avoid false-positive results, the ELISA-TB test was always performed before the Mantoux skin test. We used microbiological testing and histological examination to confirm the diagnosis of OT. Specimens submitted for microbiological testing included material obtained by sinus track, needle aspiration, or arthroscopic biopsy (four cases). The material was used to culture M. tuberculosis and for direct smear Ziehl–Neelsen staining for acid-fast bacilli. Histological examination was carried out on samples obtained by needle (8 or 11 G needle) aspiration or arthroscopic biopsy. Epithelioid cell granulomas and caseating necrotic background were considered adequate histological evidence of tuberculosis. The total diagnostic delay until start of treatment was calculated summing the patient delay (i.e. a period from the first symptom of the patient to his/her first contact with the health care provider) and the doctor delay (i.e. a period from the first contact with the physician to the start of treatment).

Finally, the trend of ascertained notifications of tuberculosis for the 1996–2004 period was obtained from ASL NA 1 (the local health agency of Naples city) to assess the dynamics of OT incidence in Naples area. The uptake area of the University Federico II Teaching Hospital includes more people than the population registered in ASL NA 1 (about 1,100,000 inhabitants), but this agency provides health to the whole urban area of Naples where most of the tuberculosis cases occur.

Statistical analysis

An analysis of variance was used to compare diagnostic delays between decades of admission. The differences were checked by Bonferroni tests. A Chi-square test was used to evaluate differences in the distribution of confirmed OT cases with respect to categorical explanatory variables. Univariate and forward stepwise linear regression analyses were used to determine whether explanatory variables were significantly associated with the total or doctor diagnostic delay. The influence of explanatory variables on the rate of confirmed OT was checked by univariate and multiple logistic regression analyses. The explanatory variables included in the models were age (continuous), gender (categorical: 0 = female; 1 = male), decade of admission to the hospital (categorical: 1 = 1975–1984; 2 = 1985–1994; 3 = 1995–2004), nationality by birth (categorical: 0 = immigrant; 1 = native Italian), and diagnostic use of MRI (categorical: 0 = no; 1 = yes), CT (categorical: 0 = no; 1 = yes), or ELISA-TB test (categorical: 0 = no; 1 = yes). All explanatory variables were included in multiple regression models, independent of their significant association with the outcome of interest at the univariate analysis.
A value of \( p < 0.05 \) was considered significant. Data were analysed using SPSS software (Chicago, IL, USA).

**Results**

The incidence of extrapulmonary tuberculosis and OT per 100,000 inhabitants and its 1996–2004 dynamics in Naples city are shown in Fig. 1. The incidence of ascertained extrapulmonary tuberculosis and OT in this period was 0.85 and 0.18 per 100,000 population, respectively. OT represented 19.2% out of all notifications for extrapulmonary tuberculosis.

In the 1975–2004 files of our hospital, 136 patients with a diagnosis of OT were identified. Polyarticular disease was diagnosed in three patients (2.2%), in whom there was simultaneous or progressive involvement of different skeletal sites. Both hip and shoulder were affected in one case, hip, elbow and foot in the second, and thoracic spine and knee in the third. Thus a total of 140 lesions were studied. Fifty-three cases were diagnosed from 1975 to 1984, 36 cases from 1985 to 1994, and 47 cases from 1995 to 2004. The frequency of OT out of the total admissions to our hospital in the decades under consideration is reported in Table 1. Eleven patients (8%) were from high-incidence areas outside of Italy (i.e. incidence greater than 50 per 100,000/year) and eight of them were admitted to our hospital in the last decade, leading to 16.6% prevalence of immigrants in this period. Sixty-three patients (46.3%) were women and 73 (53.7%) were men. The mean age at diagnosis was 47.5 years (9–81), 32 of the patients (23.5%) were in the 51–60 age decade, and two cases were observed in children younger than 10 years. The oldest patient was 81. Anti-HCV antibodies were detected in six patients (15%) out of 40 who underwent this diagnostic testing. No one was HIV positive. The location of the infection is reported in Table 2. The spine was the most common site, and the thoraco-lumbar junction was affected in 13 cases (9.3%). In one patient, active pulmonary tuberculosis was simultaneously present, and 33 patients (24.3%) reported previous pulmonary or extrapulmonary infections. The total delay until start of treatment averaged 216.6 days (5–133). In two women who were observed during the decade 1975–1984, the start of treatment was particularly delayed. Association of tuberculosis of the shoulder with rheumatoid arthritis and tubercular involvement of the elbow (with negative diagnostic tests) were diagnosed in these two cases with a delay until start of treatment of 133 and 125 days, respectively. The total diagnostic delay was shorter in the last decade of admission compared to the previous two decades. Indeed, it was 252 ± 173 days in the 1975–1984 decade, 217 ± 148 days in the 1985–1994 decade, and 176 ± 153 days in the 1995–2004 decade (\( p = 0.065 \)). The difference between first and third decades was almost significant (\( p = 0.059 \)). The doctor delay was significantly reduced (\( p = 0.004 \)) in patients admitted in the third decade (17 ± 12 days) compared to those admitted in the first decade (31 ± 26 days).

Pain, low-grade fever, and loss of weight were the most common presentation symptoms with 85%, 67.8% and 37.1% prevalence, respectively. A cutaneous sinus or ulcer was observed in 16 lesions (11.4%). Neurological involvement was present in 11 cases out of 79 spinal lesions (13.9%). Stage I (six patients), Stage II (three patients), or Stage III (two patients) neurological involvement was diagnosed in 11 patients. None were found to have Stage IV neurological involvement.

On admission, the average first hour erythrocyte sedimentation rate (ESR) was 45.3 mm/h (4–142). Eleven patients (8.1%) had an ESR slower than 20 mm/h. The leucocyte count was normal in 93 cases (68.4%), whereas leucopenia and leucocytosis were found in 31 (22.8%) and in 16 (11.8%) patients, respectively. Relative lymphocytosis with inversion of the leucocytary formula was found in 18 days (5–133). In two women who were observed during the decade 1975–1984, the start of treatment was particularly delayed. Association of tuberculosis of the shoulder with rheumatoid arthritis and tubercular involvement of the elbow (with negative diagnostic tests) were diagnosed in these two cases with a delay until start of treatment of 133 and 125 days, respectively. The total diagnostic delay was shorter in the last decade of admission compared to the previous two decades. Indeed, it was 252 ± 173 days in the 1975–1984 decade, 217 ± 148 days in the 1985–1994 decade, and 176 ± 153 days in the 1995–2004 decade (\( p = 0.065 \)). The difference between first and third decades was almost significant (\( p = 0.059 \)). The doctor delay was significantly reduced (\( p = 0.004 \)) in patients admitted in the third decade (17 ± 12 days) compared to those admitted in the first decade (31 ± 26 days).

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**Table 1** Frequency of 1975–2004 OT admissions to the Department of Orthopaedic Surgery of Federico II University Hospital, Naples, divided by decade

<table>
<thead>
<tr>
<th>Decade</th>
<th>Total admissions</th>
<th>Cases of OT</th>
<th>OT frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975–1984</td>
<td>11,065</td>
<td>53</td>
<td>0.48</td>
</tr>
<tr>
<td>1985–1994</td>
<td>25,128</td>
<td>36</td>
<td>0.14</td>
</tr>
<tr>
<td>1995–2004</td>
<td>25,335</td>
<td>47</td>
<td>0.19</td>
</tr>
</tbody>
</table>

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**Table 2** Frequency of 140 OT lesions seen at the Department of Orthopaedic Surgery of Federico II University Hospital, Naples, from 1975 to 2004

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>79 (56.4%)</td>
</tr>
<tr>
<td>Hip</td>
<td>24 (17.1%)</td>
</tr>
<tr>
<td>Knee</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Sacroiliac</td>
<td>6 (4.3%)</td>
</tr>
<tr>
<td>Foot</td>
<td>6 (4.3%)</td>
</tr>
<tr>
<td>Elbow</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (3.6%)</td>
</tr>
</tbody>
</table>
patients (13.2%). Ninety-five patients (69.8%) had an indurative response wider than 10 mm at the 48 h reading of the Mantoux skin test, whereas 41 patients (30.1%) were totally negative. When the presence of IgA or IgG antimycobacterial antibodies was evaluated with an ELISA-TB test, positive results were obtained in 43 out of 59 patients (72.9%).

Juxtaarticular osteopenia, bone erosion, soft tissue swelling, and/or narrowing of the joint space were detected in the baseline radiographs of 57 of 61 (93.4%) non-spinal lesions. Narrowing of the disc space and simultaneous rarefaction or destruction of neighbouring endplates was observed in 76 cases (96.2%) of spinal tuberculosis. In three cases (3.8%), atypical spinal involvement was diagnosed: in two cases, there was contemporary involvement of two adjacent intervertebral disc spaces; and in one case, two distant vertebral bodies were simultaneously affected.

Technetium (99m) methylene diphosphonate (Tc-99m MDP) bone scans were obtained from 83 patients with 84 lesions; 71 of these confirmed the spinal tuberculosis. Increased uptake in the affected area was noted in 72 lesions (85.7%). CT scans were available from 78 lesions (55.7%) before 1993 and this method was used as a guide for percutaneous biopsy or to drain paraspinal abscesses in seven patients with an 8-G needle. Since 1993, MRIs have been available for all OT lesions (51 cases, 36.4%). Intra- or para-articular cold abscesses were found in 23 lesions (45%). In these cases, hyper-intensity on T2-weighted images with a peripheral hypo-intense rim and hypo-intensity on T1-weighted images with a peripheral hyper-intense rim were noted. Post-enhancement images were also present. In 34 spinal lesions (66.7%) examined by MRI, heterogeneous signal intensity with a rim enhancement pattern along with anterior corner destruction and subligamentous spread were detected. In 17 cases with peripheral skeletal involvement, synovitis with synovial hypertrophy, bone marrow oedema and bone erosion were typically detected.

Percutaneous needle biopsy was performed in all patients. In four patients this investigation as well as blood and skin tests were all negative, and therefore an arthroscopic biopsy was carried out. Positive histology was found in a total of 97 lesions (69.3%), whereas microbiological examinations (mycobacterial culture and Ziehl–Neelsen stains) were positive in 57 lesions (40.7%). The arthroscopic biopsies yielded positive results even if the histological examination of material obtained by needle aspiration was negative. The rate of bacteriologically or morphologically confirmed OT was higher among the patients admitted in the third decade (77%) with respect to those admitted in the first (64%) or second (64%) decade, though this difference was not significant. In 43 (30.7%) lesions with high clinical and laboratory suspicion, a confirming diagnosis could not be made, despite repeated histological and microbiological examinations. In these cases chemotherapy was nevertheless initiated.

In our study group several factors were associated with a shorter total diagnostic delay at the univariate analysis. They included the diagnostic use of MRI (p = 0.028), more recent decade of hospital admission (p = 0.021), and the Italian nationality by birth (p < 0.001). Both decade of admission (p = 0.001) and Italian nationality by birth (p < 0.001) had significant inverse association with the total diagnostic delay in a model of multivariate regression analysis. At the univariate analysis, a more recent decade of admission (p = 0.002) and the diagnostic use of CT (p = 0.033), MRI (p = 0.002), or ELISA-TB test (p = 0.002) were inversely associated with the doctor delay. ELISA-TB test was the only diagnostic test associated with a shorter doctor delay when all variables were included in a model of multivariate regression analysis (p = 0.001). No factor influencing the rate of diagnostic confirmation was discovered at the logistic regression analysis.

Discussion

The incidence of tuberculosis in Italy decreased over 1970s and 1980s, but since late eighties it started to increase again, and this increase particularly concerned extrapulmonary lesions. Afterwards, tuberculosis cases in Italy decreased from 10 per 100,000 in 1995 to 7 per 100,000 in 2004. The incidence of pulmonary and extrapulmonary cases was 7 and 2.5 per 100,000, respectively, in 1995, and 5 and 1.8 per 100,000, respectively, in 2004. In the 1995–2004 decade, extrapulmonary tuberculosis accounted for 25% of all tuberculosis cases and OT represented 5% of all extrapulmonary lesions. In the same period in Naples city the incidence was 7.0 per 100,000 and 1.0 per 100,000 for overall tuberculosis and extrapulmonary lesions, respectively. No published data on the incidence of OT in the study area are available, but we obtained the 1996–2004 notifications from the local health agency of Naples city. To the best of our knowledge, no previous study reported such data. The 1996–2004 OT incidence in Naples was substantially stable and averaged 0.18 cases per 100,000/year, similar to the incidence reported in native Dutch. However, since no information on the former period is available, it is difficult to find out whether the slight increase in OT admissions observed in our hospital in the last decade reflects a simultaneous increase in the OT incidence or other uncontrolled local factors.

In other European countries the recent increase in the incidence of OT is attributable to immigration from high incidence areas. The proportion of legal immigrants on the total population also raised in Naples area from 1995 (0.4%) to 1998 (0.7%). In the same period the incidence of pulmonary tuberculosis in Campania increased from 2.75 per 100,000 in 1995 to 4.04 per 100,000 in 1996 and reached a peak in 1999 (4.67 per 100,000 in Campania region and 7.27 per 100,000 in Naples area). Afterwards, the incidence decreased and stabilised at nearly 3 cases per 100,000 inhabitants in the 2002–2004 period. The majority of cases always occurred in Naples city. The small percentage of legal foreign-born citizens cannot be the only responsible for the increase in the incidence of pulmonary tuberculosis from 1995 to 1999, but illegal immigrants may have contributed to the diffusion of tuberculosis. Indeed, since they are less likely to access public hospitals, they elude health service surveys and so their influence on the epidemiological data is negligible. The number of immigrant cases also increased in our hospital in the last decade, but it was small in relative terms and thus most cases were diagnosed in native Italians. This result is in...
keeping with a study from the same area. As shown in previous studies, overcrowding and immigration from high-incidence countries may have concurred to cause the increase of tuberculosis in the study area from 1995 to 1999. Indeed, when the latest national census was carried out the mean population density was 189.14 inhabitants/km² in Italy, whereas in the Naples area it was 2612.97 inhabitants/km². A study from Naples city showed that overcrowding is independently associated with the incidence of tuberculosis in a model of multivariate analysis. Moreover, the effect of crowding, manifested predominantly in overcrowded settings, has been found to account for much of the increased risk of tuberculosis previously associated with race and ethnicity. HCV infection also may have played a role, since this infection, which is prevalent in Naples area, was also overrepresented in our patients. A high frequency of tuberculosis in HCV patients has been reported previously, although the reason for this association is unclear. Inefficiency of the cellular immune response in chronically HCV-infected persons has been reported and a previous epidemiological study pointed to immunodepression as the cause of increased susceptibility to OT in persons living in large metropolitan areas.

The proportion of false negative skin tests in our patients was high. However, 50% of patients with extrapulmonary tuberculosis confirmed by histological testing or microbiology had false negative results of Mantoux test in one previous study from Naples area. Our result could be explained by coexisting debilitating illnesses affecting our patients on admission that provoked lack of reactivity on skin tests carried out within 48 h. The selected 10 mm cut-off also may have contributed to lessen the sensitivity of skin tests. In patients with negative skin tests the diagnosis of OT was always confirmed by histological testing, microbiological testing, or ELISA-TB test before the treatment was started.

In areas where the disease is not prevalent, biopsy is mandatory in order to make diagnosis of OT. Positive microbiological and histological yields can be obtained in 64–90% of all patients; our results also fall in this range. As in previous studies, microbiological testing proved to be less sensitive than histology. Even with these additional diagnostic examinations, we could not confirm the diagnosis of OT in roughly one-third of our patients. Following a previous recommendation, we nevertheless started empirical antituberculosis treatment in those patients with a high index of clinical suspicion. A prospective monitoring study covering 21% of all TB cases notified every year in Italy reported a rate of bacteriological confirmation of 68.3% in extrapulmonary cases and concluded that such a rate was sub-optimal. On this basis, we believe that the proportion of OT diagnostic confirmation should also be increased in our hospital. However, we observed a trend toward an improvement in the rate of confirmed diagnosis over decades, even though we could not identify any factor related to this diagnostic improvement at multivariate analysis. We hypothesize that the confirmation rate was increased in dynamics by more skilled doctors.

The 31-week total diagnostic delay to the diagnosis of OT in our patients is equal to the results of another European study. The rarity of OT in developed countries and its non-specific clinical manifestations, in conjunction with the poor awareness of treating physicians, all may contribute to this delay in diagnosis of the disease, resulting in increased damage to the spine and peripheral joints. In our hospital both total diagnostic and doctor delays were reduced in patients admitted in the third decade compared to those admitted in the first decade. The total diagnostic delay was shorter in native Italians than in foreign-born citizens. This result can be explained by difficult access to health facilities of recent immigrants. Since 1992, we have been performing ELISA-TB tests to identify specific anti-tubercular antibodies. This test is not very sensitive, but it has a specificity higher than 90%, which is better than that of skin tests. It is a useful diagnostic tool in OT tuberculosis, especially if molecular techniques are not available. In the current study, the measurement of IgG and IgA against A60 was the only test associated with a reduction of doctor delay in OT diagnosis at multivariate analysis. Because of its high specificity, the A60 based serological testing could be useful in cases with negative results of microbiological and/or histological examinations.

In conclusion, the OT incidence was steadily low in our geographic area over the last decade. During the same period, the number of admissions for OT slightly increased in our hospital and most cases were diagnosed in native Italians. Thorough and even invasive diagnostic work-up is mandatory for the proper and timely management of patients with OT. We always used microbiological testing and histological examination to confirm the diagnosis of OT. Even in the absence of positive results, empirical antituberculosis treatment was nevertheless initiated in many of our patients with high clinical suspicion in order to limit the potentially permanent destruction of affected skeletal segments. ELISA-TB test can be a useful diagnostic tool since it is associated with a reduction in the diagnostic delay.

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References


