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Disseminated Mycobacterium Bovis Infection in an Immunocompetent Host

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Abstract
We report about a rare case of disseminated *Mycobacterium bovis* infection in a 61 year old female immunocompetent patient with involvement of the lung, the brain, the spleen and spine. The patient had intracerebral tuberculomas with paradoxical enlargement during the first weeks of therapy. We reviewed the data of our microbiological department and found five other patients with *Mycobacterium bovis* infection diagnosed between 1999 and 2004, which are 5.8 % of all diagnoses of tuberculosis during this period.

Key words: Mycobacterium bovis, disseminated infection, immunocompetent patient, intracerebral tuberculomas, central Europe

Abbreviations: AFB: acid-fast bacteria, PZA: pyrazinamide, BAL: bronchoalveolar lavage, ABPA: allergic bronchopulmonary aspergillosis

Introduction

Before establishing effective control measures for bovine tuberculosis *Mycobacterium bovis* (M. bovis) infections were a common cause of extrapulmonary tuberculosis in children, transmitted by unpasteurized milk. In Western Europe and North America this presentation of disease has almost vanished. In 1952 a program to fight bovine Tuberculosis was started in Western Germany. By that time only 10% of the cattle herds were free of tuberculosis after ten years this proportion had risen to 99.7% [1]. Eastern Germany was declared free of bovine tuberculosis in 1978. It is estimated that in the 50th of the last century approximated 10-30% of all TB cases in Germany were caused by M. bovis, nowadays it is approximately 1 %, most of them are considered to be reactivations [2].

We report on six cases with M. bovis infections diagnosed in our institution between 1999 and 2004 which represents 5.8 % of all diagnoses of tuberculosis during this period. Patients are older than 55 years, which means that they grew up in a time when tuberculosis in cattle was still prevalent in Central Europe. So even decades after eradication of bovine tuberculosis M. bovis infection still exists in the local population.

Case Report

Case one is a 61 year old female patient. Five months before being referred to our department the patient was the first time admitted to a country hospital with restlessness, anxiety, amnesic aphasia and a weight loss of 7 kilograms. Because of a seizure two weeks later a cranial CT scan was done and showed a hypodense left parietal cerebral tumor with extended perifocal edema, which was supposed to be a metastasis or a brain tumor. The tumor was resected and histologic examination revealed a granulomatous inflammation with necrosis and vasculitis but without detection of mycobacteria including PCR. A CT scan of the thorax and abdomen showed no abnormalities. Because of persisting fever an antimicrobial treatment was started but showed no lasting success. CT of the thorax was repeated a few weeks later. This time micronodular infiltrations were seen in both lungs. Tuberculin testing was negative. A CT scan of the abdomen now revealed multiple hypodense nodules in the spleen and several enlarged paraaortal lymph nodes. A biopsy of the spleen demonstrated granulomatous inflammation. Disseminated sarcoidosis was suspected and steroid therapy was initiated. Two days later the patient was transferred to our institution because of worsening of the general condition.

On admission the patient was disoriented, tachypnoic and had a temperature of 38.2°C. Haemoglobin was 11.2 g/dl and leukocytes 9400 /ml. She had elevated liver enzymes (AST 46 U/l, ALT 35 U/l, gGT 383 U/l, AP 318 U/l) and a slightly elevated CRP (9.6 mg/l). No evidence of immunodeficiency (immunoglobulin levels, lymphocyte subpopulations, HIV test) were found.

Because either disseminated sarcoidosis or tuberculosis was possible, glucocorticoid therapy (100 mg/d) was continued and an antimycobacterial therapy with isoniazid, rifampin, ethambutol and pyrazinamide was initiated. Ziehl-Neelsen stains and M. tuberculosis complex PCR (COBAS AMPLICOR MTB system, Roche Diagnostics, Mannheim, Germany) from bronchoalveolar lavage and tracheal secretions were repeatedly negative, but PCR from stomach secretions was once positive (this sample being culture negative). BAL differential cell count revealed an increased pro-

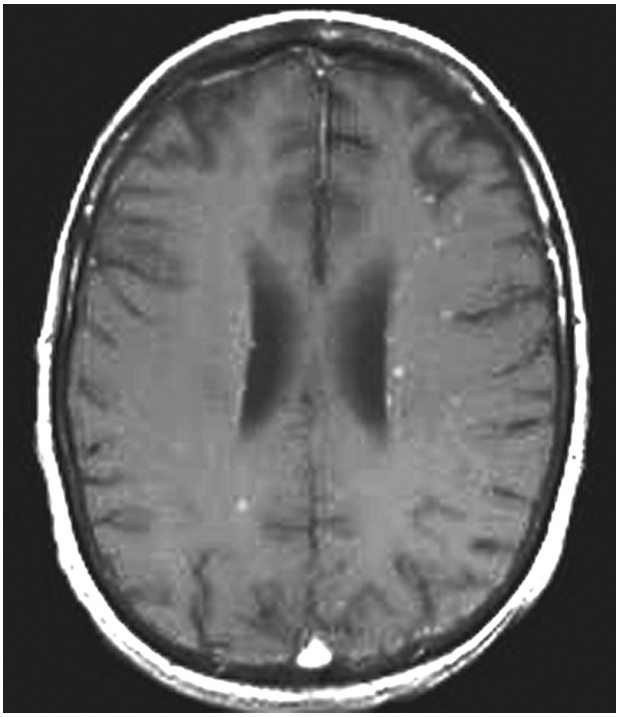

Fig 1. First MRI revealing multiple small contrast enhancing nodules representing intracerebral tuberculous granulomas. Lack of meningeal enhancement indicates that granulomas can occur without meningitis.

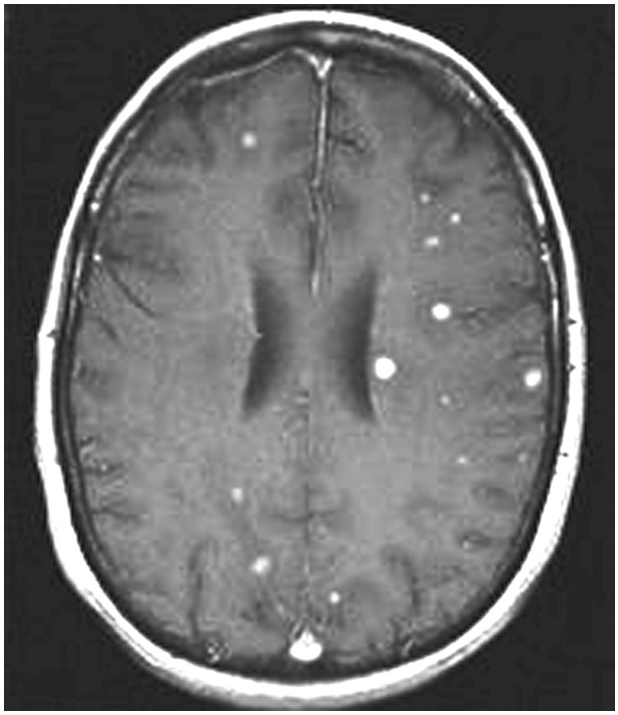

Fig. 2. Follow up examination 9 weeks after initiation of antimycobacterial treatment shows increase of the intracerebral granulomas in number and size.

Table 1. Clinical features of the six patients with *Mycobacterium bovis* infection.

case	age, gender	site of infection	site of isolation	AFB smear	PCR	culture	PZA sensitive	Underlying condition
1	61, female	disseminated	BAL	neg.	neg.	pos.	-	none
			stomach secretion	neg.	pos.	neg.		
2	59, female	urinary tract	urine	neg.	pos.	pos.	-	none
3	75, female	mamma	puncture of abscess	neg.	not done	pos.	+	none
4	82, female	left elbow	puncture of joint	neg.	neg.	pos.	-	none
5	84, male	lung	sputum	neg.	pos.	pos.	-	Colon carcinoma
6	77, male	pharynx, larynx, lung	sputum	pos.	pos.	pos.	+	ABPA, steroid therapy

portion of lymphocytes (31%). On a cranial MRI there were multiple disseminated intracerebral lesions with a size of some millimetres without any signs of meningitis (Fig. 1). A lumbar puncture showed slightly increased leukocyte count (7/mm^3), mainly mononuclear cells, protein was 167 mg/dl, glucose 30 mg/ml and lactate 40,5 mg/ml. Gram and Ziehl-Neelsen stains were negative as well as M. tuberculosis complex PCR. MRI of the spine revealed spondylodiscitis of the thoracic vertebrae 11 and 12. Four weeks later mycobacterial culture from the BAL became positive and M. bovis was identified which was sensitive to all tested drugs except pyrazinamide. Streptomycin was substituted for pyrazinamide. An MRI performed 9 weeks after the initiation of antimycobacterial treatment showed an increase of the intracerebral tuberculomas (Fig. 2). Steroid therapy was restarted and the size of the tuberculomas decreased after 2 weeks. The patient recovered uneventfully. On repeated examination the patient reported that in the 1950th she lived for several years on a farm in the north eastern part of Germany where unpasteurized milk was ingested routinely. She remembered bovine tuberculosis in some neighbouring farms, but the patient had no individual or family history of tuberculosis.

Table 1 shows the clinical and microbiological features of all six patients. Four patients had a history of growing up in rural areas with former epidemic bovine

tuberculosis. In four cases the first suspected diagnosis was a malignancy. All six isolates were sensitive to isoniazid, rifampin, ethambutol and streptomycin and two of the six strains were sensitive to pyrazinamide. PCR which was performed in five of the six culture positive samples showed positive results in only three cases. One patient had a diagnosis of colon carcinoma and died some weeks later. Another patient had allergic bronchopulmonary aspergillosis and was on steroid treatment when tuberculosis was diagnosed. The other four patients had no evidence for immune deficiencies or severe comorbidities. Five patients had extrapulmonary manifestations. Except of patient 5 all recovered uneventfully with antituberculous chemotherapy for 6-12 months.

Discussion

M. bovis has one of the broadest host ranges of all known pathogens [3]. In developed countries the classical manifestation with infection of the cervical lymph nodes and the gastrointestinal tract has become very rare. This may be different in populations with a high percentage of immigrants from countries with incomplete control measures. However even in developed countries elimination of bovine TB is often incomplete because of the spread of infection from wild animals to domestic cattle. Infection from cattle to human is also possible by the respiratory route in slaughterhouse or farm workers leading to primary pulmonary tuberculosis [3]. Human to human transmission of M. bovis was confirmed only in rare cases, but it does occur in patients with immunodeficiency [4, 5]. Thus, the role of the HIV/AIDS pandemic on the epidemiology of M. bovis has caused some concern [6].

Nowadays the most common sites of infection are the lung, the genitourinary tract, bones and joints and the central nervous system. As confirmed in our series extrapulmonary manifestations are more common in M. bovis than in M. tuberculosis infection [7]. 2-4% of M. bovis infections are meningeal infections [6], but to our knowledge there are only two case reports about intracerebral tuberculomas in M. bovis infection. Despite antituberculous treatment both patients died within a few weeks [8, 9]. Disseminated infection has been observed in patients with immunodeficiency. In contrast, there is only scarce evidence of disseminated infection in immunocompetent patients in the literature [10, 11]. In a study done in San Diego between 1980 and 1991 9 out of 48 patients with M. bovis infection had disseminated disease, all but one being HIV positive [7].

Patient 1 in our series showed multiple intracerebral tuberculomas which increased in size and number during the first nine weeks of antimycobacterial treatment. This paradoxical enlargement has been described before in M. tuberculosis infections [12]. It normally occurs within the first three months of treatment and should not be misinterpreted as a treatment failure. The pathogenesis of this phenomenon is not fully understood, but the most likely explanation is an interaction between the host´s immune response and mycobacterial products. In a review of 40 patients with M. tuberculosis infection and paradoxical enlargement of intracerebral tuberculomas steroids appeared to alleviate neurological symptoms and to improve the outcome [12]. The fact that in our case report tuberculomas decreased only two weeks after restarting high dose steroid therapy confirms the benefits of this adjunctive approach.

M. bovis subsp. bovis is intrinsically resistant to pyrazinamide, while M. bovis subsp. caprae is pyrazinamide susceptible. In Germany one third of M. bovis strains belong to M. bovis subsp. caprae. This probably explains the sensitivity to pyrazinamide of two of our isolates. This subspecies is very rare in most countries [2]. As in our series in most studies primary resistance of M. bovis to the other first line antituberculous agents is rare. In a study done in San Diego (USA) 71 M. bovis isolates were tested. 2.8 % were resistant to isoniacid, 1.4 % to rifampin, 1.4 % to ethambutol and none to streptomycin. There was no multiresistant strain [7]. However there are some recent reports about multidrug resistant M. bovis in HIV positive patients. (4,5).

In our report M. bovis infection accounted for 5.8% of all tuberculosis infections which is much higher than the estimated figure of 1% published before in our country. Thus, especially in elderly persons with extrapulmonary manifestation of tuberculosis, M. bovis infection should still be considered even in immunocompetent patients. Frequently the first suspected diagnosis is malignancy. Another valuable hint may be a history of growing up in a rural area or consumption of unpasteurized milk in the past. A rapid diagnosis is essential because this can be a life threatening infection even in patients without known immuno-deficiencies.

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