CASE REPORT

Miliary tuberculosis with atypical presentation in an immunocompetent young African man

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SUMMARY

We present an atypical case of tuberculosis in an immunocompetent man from west Africa living in Europe. The patient entered the hospital with a painful lump of 3 cm on his right clavicle which he noticed 2 weeks before and back pain. During the examinations for further evaluation his condition deteriorated within short time. Tuberculosis was diagnosed, treatment started but he needed mechanical ventilation at the intensive care unit and had kidney failure. The further involvement was favourable in the end but needed intensive treatment for over 4 weeks. Tuberculosis cases with such severe evolution are rather known with immunodeficient patients. Extrapulmonary tuberculosis, especially skeletal tuberculosis is seen more frequent in young immunocompetent migrants. The migrating persons seem to be more at risk to get sick than the ones staying in their origin country. We suppose the course of our patient's disease is miliary or septic, of which both are rather rare entities.

BACKGROUND

The patient entered the hospital in quite a good state, just reporting of a swelling on his right clavicle and a little pain in his back. The further evolvement was dramatic.^{1–9} We understood that the patient had tuberculosis (TB), but we did not understand his pulmonary deterioration, the kidney failure and affection of the liver. Already during hospitalisation we were, without avail, searching the literature for similar cases. After the patient was released from hospital care we did a thorough literature search to explain the evolvement of this case. There are different TB strains, originating mostly in western Africa, and migrating persons with a normal immune system fall sick in their new home country without any known cause. There is a rare manifestation of TB as sepsis which is usually diagnosed postmortem only.

We think this case is important as the migration of persons among different continents is common and we have to be aware and up to date of extrapulmonary TB as it is a treatable disease.

A patient's consent form could not be obtained. Data were anonymised as much as possible.

CASE PRESENTATION

A young man in his late 20s reported fatigue, recurrent fever, night sweats and weight loss for several weeks. He suffered from back pain and noticed a swelling on his right clavicle. Originating from west Africa, he has been living in Europe for several years.

The clinical examination revealed diffuse abdominal and lumbar pain and a swelling on the right clavicle of 3×3 cm, several enlarged and tender inguinal lymph nodes on both sides and an enlarged prostate. The laboratory results showed elevated liver enzymes (aspartate aminotransferase 48 U/L, alanine aminotransferase 68 U/L, alkaline phosphatase 115 U/L, γ -glutamyltransferase 117 U/L) and infectious parameters (C reactive protein 88 g/L), hyponatremia (128 U/L) and light microcytic hypochromic anaemia (haemoglobin 105 g/L, Lc 6.7 G/L, Tc 191 G/L).

INVESTIGATIONS

In the biopsy of the bones (vertebra and iliac bone) *Mycobacterium tuberculosis* had been isolated classifying this case as an extrapulmonary TB (because the sputum smears were negative for TB) with multifocal bone affection.

Conventional radiological imaging of the thorax was normal (figure 1). The CT scan (figures 2 and 3) showed multiple lesions: right clavicle, 12th rib, different vertebral bones of the thoracolumbar segments without discitis or myelocompression and both iliac bones. Furthermore, there were two spots in the upper left lobe of the lung, enlarged lymph nodes (mediastinal, para-aortic) and hypodense lesions in the liver (three segments, ie, I, VII and VIII) and an enlarged prostate. QuantiFERON test of the blood was positive but smear and PCR of the sputum were negative.

DIFFERENTIAL DIAGNOSIS

Serological testing for HIV, *Treponema pallidum*, hepatitis, toxoplasmosis, Epstein-Barr virus,

Figure 1 X-ray of the thorax at the time of hospital admittance.

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Figure 2 CT of the thorax/spine/pelvis at the time of diagnosis (bone lesions marked with arrows).

Cytomegalovirus, *Salmonella*, *Shigella* and *Campylobacter* was negative.

TREATMENT

Drug therapy with four substances (rifampicin, isoniazid, pyrazinamide and ethambutol) was installed.

OUTCOME AND FOLLOW-UP

Two days after starting treatment, the patient presented a respiratory distress syndrome and had to be transferred to the intensive care unit (ICU) for mechanical ventilation. Radiological and clinical findings confirmed an acute respiratory distress syndrome (ARDS)-like syndrome (figure 4).

Bronchoalveolar lavage was consistent with lymphocytic alveolitis but a Ziehl-Neelson stain of the bronchoalveolar fluid was negative. Results of the later on positive sputum and lavage cultures were pending at that time.

Additionally a broad-spectrum cephalosporin and intensive diuretic treatment were administered. Liver enzymes were 100-fold elevated and decreased gradually during the treatment. During the stay in the ICU, kidney function deteriorated and the dosage of the tuberculostatic therapy had to be reduced. Renal biopsy showed chronic interstitial nephritis (probably due to analgesia with metamizol, contrast agent during the CT scan or rifampicin), requiring the administration of a concomitant steroid therapy. Already after 3 days his respiration recovered and he was transferred back to the ward. The patient was in a poor condition and kept on complaining about his back pain.

After 4 weeks he had recovered and was able to manage his daily activities.

However, he was still complaining about back pain. The radiological control showed an instable vertebra at the fourth lumbar level (figure 5). The question that arose was whether surgical intervention had to be performed and if so, at which

Figure 3 Detail of CT of the lumbar spine.

Figure 4 X-ray of the thorax with acute respiratory distress syndrome-like pattern.

time point. In the literature no similar case has been described: in India and mostly in developing countries only patients with huge gibbus and neurological symptoms necessitate obvious surgical intervention. In one report, alendronate had been administered together with tuberculostatic therapy.¹⁰ The major challenge of this unique case was to opt for a therapeutic strategy without being able to refer to published literature. Surgical stabilisation and vertebroplasty were performed (figure 6) after 2 months of tuberculostatic therapy.

Therapy was reduced to three drugs after 3 weeks because the pathogen was sensitive to common tuberculostatic drugs; the whole therapy lasted for 9 months.

Radiological control after 9 months showed only the hypodense lesions in the liver which were interpreted as cysts. Steroid therapy was administered for over 6 months and then slowly reduced. Kidney function returned to normal.

Figure 5 CT of the lumbar spine after a 2-month course of tuberculostatic therapy.

Figure 6 X-ray of the lumbar spine after stabilisation.

DISCUSSION

Initially the diagnosis was consistent with extrapulmonary TB but it had to be revised because an acute deterioration of the patient's general condition occurred. The respiratory function deteriorated rapidly and the patient needed mechanical ventilation transiently. The bronchoalveolar lavage was negative for TB but cultures turned out positive. Liver and kidney function deteriorated temporarily. The patient was septic either because of the miliary spreading of TB or because of a concomitant sepsis, also called Landouzy sepsis. This is a rare entity, described first at the end of the 19th century, and was also called 'sepsis tuberculosa acutissima'. It presents with three patterns of evolution: first, a typhoid septic form with early exitus; second, a typhoid sepsis followed by a short symptom-free interval, followed by multiorgan failure with exitus and a third pattern, a septic presentation followed by a complete recovery.¹¹

In the majority of the cases reported in the literature, the diagnosis has been made only postmortem confirming the confusing clinical picture of this disease.^{12–18}

To recapitulate the pathogenesis of TB based on diagnostic standards and classification of the American Thoracic Society: an infection with *M tuberculosis* starts in the lung where

alveolar macrophages ingest the bacteria. The microorganisms grow slowly inside the macrophages and do not trigger an immune response in the beginning. In a further step, they spread through the lymphatic system first, then via blood circulation. Specific antibodies are then produced against the pathogen, but do not seem to be protective. Especially in the upper segments of the lungs, in the kidneys, bones and brain, the environment seems to be favourable for the proliferation of the bacteria. Other organs such as the bone marrow, liver and spleen are usually infected but bacteria do not proliferate well in these environments. In this stage the infection can only be diagnosed by skin or QuantiFERON tests because at this time point patients are asymptomatic and radiological and other blood tests are not specific. The real cause and the time point triggering a breakthrough of the infection remains unclear. At this step, clinical symptoms are unspecific: fever, night sweats, weight loss, weakness.

Infection of the spine occurs either through haematogenic spreading usually from the lung and/or via a lymphogenic pathway through para-aortic lymph nodes. Usually more than one vertebra is involved. However, the infection is not pyogenic (no proteolytic enzymes are secreted) but leads to a delayed hypersensitivity reaction with the formation of granulomas. The bone destruction starts usually at the anterior part of the vertebra, close to the vertebral plates.⁷

American and European studies reported extrapulmonary TB occurring together with concomitant pulmonary affection. This form of disease is found mainly in young immunosuppressed patients and older patients between 60 and 70 years of age. In contrast, our patient did not show any pulmonary symptoms initially and was a young immunocompetent man. Only his multifocal skeletal foci and their atypical pattern correlate with previous publications of immigrants from Africa and Asia.^{19–22}

For our patient, another scenario had to be taken into account: a paradoxical reaction to tuberculostatic drugs, which occurs usually only 3–8 weeks after start of treatment²³ and refers mostly to the clinical or radiological worsening of pre-existing tuberculous lesions.

The review of the literature showed only few cases with similar patterns: Murray *et al*²⁴ described three cases with a fulminant pneumonia but all cases started with primary infection. Another report presented a case with miliary TB, initially without affecting the lungs but later on, complicated by an ARDS. In the beginning, elevated liver enzymes as well as blood dyscrasia were reported and *M tuberculosis* was isolated in the cerebrospinal fluid, confirming the diagnosis. The patient, a 60-year-old Japanese woman, died 3 days later.²⁵

This seems to be one of the rare cases having developed an ARDS as a complication of miliary TB without having any other comorbidity.²⁶ In other reports, patients with miliary TB and ARDS almost had predisposing factors such as alcohol abuse, diabetes, hepatic cirrhosis, etc.²⁷ High mortality rates have been reported in patients with acute respiratory failure on the background of pulmonary TB.²⁸

The elevated liver enzymes might be due to a paradoxical reaction to the drugs or due to the effect of the tuberculostatic drugs themselves. The latter scenario is less conceivable because the enzymes normalised despite permanent tuberculostatic therapy. Miliary TB is more probable because it has been shown that hepatic TB is usually present in all miliary TB cases.²⁹ It has been found in 80–100% of autopsied patients with disseminated pulmonary TB.³⁰

The kidney failure had multiple causes: first, contrast agent had been used for the CT scan of the lungs; second, analgesic

treatment (metamizol) and also rifampicin had been administered. The histological pattern showed diffuse chronic tubulointerstitial nephritis without any granulomas. Acute nephropathy may occur with all four tuberculostatic drugs but mostly with rifampicin. Usually acute renal failure develops on reintroduction of the drug or during intermittent therapy rather than during continuous therapy.³¹

At this point we were prone to conclude that the patient had a tuberculous sepsis (third pattern as described above) but still a miliary course complicated by a paradoxical reaction to the drugs was possible. To differentiate further we were looking for additional factors that might influence the evolution of our patient's disease such as the genetic strain of TB, the origin of our patient and the vitamin D level.

Gagneux *et al*³² could demonstrate that there are at least four main strain lineages of TB associated with particular geographic regions. The evolution of TB is believed to have started as a zoonosis in Africa. An excursion into the field of global phylogeography of *M tuberculosis* shows that this bacterium is understood as a complex group of microorganisms, consisting of seven strains which are geographically dispersed. The different strains vary genetically in a very low percentage from each other, a sign that their age is not more than 20 000–35 000 years and that they have a common ancestor.¹⁰ Nevertheless the different strains explain the different distribution of TB phenotypes. Specific deletions in the genome explain different answers of the immune system in humans. TB spread to the other continents and adapted throughout time. Laifer *et al*,³³ Ramos *et al*³⁴ and French *et al*²³ investigated native populations and immigrants or foreign-born residents and found different patterns of TB. Apparently people from east Europe tend to present inactive TB, mostly due to multiresistant microorganisms, compared with immigrants from Africa who present rather pulmonary TB. Several authors, Kong *et al*,³⁵ Caws *et al*,³⁶ Cowley *et al*³⁷ and Glynn *et al*³⁸ found out that the Beijing strain is the most frequent, occurring also in the USA and Europe and seems to be associated with extrapulmonary TB and drug resistance.

It seems that different genotypes affect different organs and that the genetic variety of TB has an influence on the efficacy of a vaccine.¹⁰

We might postulate that our patient originating in west Africa, had an atypical TB strain and hence presented with the astonishing course. The spoligotyping³³ showed that our patient does not have the specific strain from west Africa but the frequent isolate originating from Beijing. Whether this might explain the aggressive course of the disease remains unclear.

Lillebaek *et al*³⁹ demonstrated that migrated persons tend to fall sick with TB not at a young age, as in their home countries, but as adults. The reasons for these differences remain unclear. Different environment as well as genetic adaptation of the bacteria might influence the time point of the onset of the disease.

Vitamin D is an immunomodulating factor activating macrophages and hence blocking the growth of *M tuberculosis*.⁴⁰ Gibney *et al*⁴¹ investigated a group of immigrants in Australia suffering from TB. Patients suffering from latent TB had normal vitamin D levels; patients developing active disease had low vitamin D levels. The authors postulated that the low vitamin D levels favour the development of an active infection. However, our patient's vitamin D level was normal.

Finally, we conclude that the most conceivable explanation of this case is skeletal TB with miliary spreading and development of ARDS and kidney failure in an immunocompetent man, having migrated from west Africa to Europe.

Learning points

- ▶ Tuberculosis (TB) has a long history as an infectious disease, but the different aspects of it are not well known among general practitioners because the cases are quite rare.
- ▶ Extrapulmonary TB occurs more often in the western world due to migration from persons mainly from Africa.
- ▶ Extrapulmonary TB outbreak is also common with immunocompetent migrated patients, the mechanism is under investigation.
- ▶ There are rare cases of tuberculous sepsis, it is important to have this in mind while treating patients with TB, as the involvement is dramatic and the outcome very often lethal.

Contributors All the authors have read and approved the manuscript. NA and BC wrote the manuscript. BC was in charge of the patient in the ward and PC corrected the manuscript.

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