Case report

Contribution to differential diagnosis of sarcoidosis and disseminated tuberculosis

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SUMMARY

A previously healthy 54-year-old ethnically Danish man was referred to the Department of Infectious Diseases at Aarhus University Hospital after an unexpected detection of *Mycobacterium tuberculosis* DNA in his lungs. Further examination revealed widespread dissemination of the tuberculosis (TB) to brain, mastoid, urinary and gastrointestinal tract. Thirteen months earlier, the patient was orchiectomised due to recurring inflammation of the right testicle. Three and a half months prior to admission to our department the patient started immunosuppressive therapy with steroids due to radiological and histological findings in the lungs that were interpreted as sarcoidosis (SA). This treatment is likely to be co-responsible for the pronounced dissemination of the TB. The patient was Bacillus Calmette-Guérin (BCG)-vaccinated as a child and had no apparent risk factors for TB apart from travelling in TB-endemic countries until 10 years before falling ill. Screening for latent TB was not performed prior to starting steroid treatment.

BACKGROUND

Due to the similar disease presentation of extrapulmonary tuberculosis (TB) and sarcoidosis (SA), TB is sometimes initially misdiagnosed as SA and vice versa.¹ TB is the second most lethal infection worldwide and thus constitutes a major global health problem.² Denmark and other Northern European countries have a low TB-incidence (5.3 per 100 000/year in Denmark in 2018),³ but disease manifestations can be grave if not properly treated. TB may be considered unlikely by Northern European physicians unless the patient is part of a high-risk group within the population, leading to delayed diagnosis and excess morbidity.

SA-incidence in Denmark is among the highest in the world at 7.2 per 100 000/year.⁴ The treatment of SA with multiorgan involvement is long-term immunosuppressive therapy with high-dose corticosteroids. If extrapulmonary TB is misdiagnosed as SA and treatment is maintained, the TB has optimal conditions for dissemination.⁵ Atypical location of extrapulmonary TB might further delay proper diagnosis, as in the present case.

The case illustrates several important learning points including raising awareness of the possibility of TB in low-risk individuals, considering extrapulmonary TB when encountering atypical inflammation patterns and revising diagnosis promptly when treatment has proven to be ineffective.

CASE PRESENTATION

Thirteen months before final diagnosis with TB, a 54-year-old previously healthy man presented at a regional hospital with a severe, recurring epididymitis with orchitis and pyocele, leading to surgical removal of a highly enlarged right testicle. Pathological examination of the testis and epididymis showed acute and chronic inflammation with focally necrotic areas, but without description of granuloma (figure 1). Three weeks after operation, the patient returned to the regional hospital with severe pain in the right leg, ultrasound showing a deep venous thrombosis. The patient received anti-coagulant therapy and was seemingly in good health upon discharge from hospital. Two months later he returned to hospital because of general fatigue and shortness of breath, both of which had gradually worsened since the deep venous thrombosis event.

Figure 1 Ultrasound showing highly enlarged right testis and epididymis with heterogenous echotexture and pyocele (top). The testis and epididymis were surgically removed, and pathology examination revealed acute and chronic inflammation of the testis and epididymis with several necrotic areas (bottom).

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Figure 2 High resolution computed tomography scan showing discrete miliary tuberculosis of the lungs. Transbronchial biopsies from the middle lobe of the right lung showed non-necrotising, granulomatous inflammation. All findings were deemed fully compatible with third stage sarcoidosis.

Figure 3 MRI of the cerebrum showing several contrast enhancing elements in hemispheres (A), the brainstem (B) and the cerebellum (C). The elements were initially interpreted as intracerebral sarcoidosis, but due to response to antituberculosis therapy, they were concluded to represent multiple tuberculoma. An abscess was seen in the left mastoid (D).

This time, a high-resolution computed tomography (HRCT) scan revealed multiple micronodular changes and consolidated infiltrations in both lungs, predominantly in the apical lobes. Respiratory medicine specialists deemed the changes fully compatible with third degree SA. A biopsy from the middle lobe of the right lung showed non-necrotising, granulomatous inflammation, which was also interpreted as SA (figure 2).

Therefore, the patient began standard SA treatment with prednisolone 37.5 mg OD, tapered to 25 mg OD after 2 months treatment. Screening for latent TB was not performed prior to starting treatment. After initiation of treatment, however, the patient's forced expiratory volume in one second (FEV₁) steadily deteriorated from 63% of the expected value at baseline to 31% 3½ months later. In the same time period forced vital capacity (FVC) decreased from 94% to 43% of the expected value, while FEV₁/FVC remained stable at around 55% of the expected value. At this point, the patient's activity related dyspnoea had progressed to dyspnoea at rest, oxygen saturation fluctuating between 88% and 90%. Additionally, he reported intermittent fever, severe headache, general fatigue and an unintended weight loss of 8 kg over the course of the past month. Renewed CT-scan revealed bilateral pulmonary embolisms as well as progression of the micronodular changes and consolidated infiltrations. Due to the patient's increasing C reactive protein (up to 147.5 mg/L), a superinfection on top of the progressing SA was suspected. At this point he reported tinnitus in the left ear and discomfort in the remaining left testicle. The ear condition progressed with pain and hearing loss, and antibiotic treatment with ciprofloxacin did not relieve symptoms from the testicle. Ultrasound of the testicle revealed a granular structure. After almost 2 weeks of antibiotic treatment had failed to clear the suspected infection, a QuantiFERON-TB test was performed. When the QuantiFERON test came back positive, the possibility of active TB-infection was considered for the first time during the patient's 1-year long disease history. A week later, bronchoalveolar lavage (BAL) fluid analysis confirmed the presence of *M. tuberculosis* in the patient's lungs. Additionally, *Pneumocystis jirovecii* was detected in the BAL fluid. MR-cerebrum showed an abscess in the mastoid as well as multiple small elements of contrast enhancement. These were initially interpreted as neurosarcoidosis, but given the discovery of pulmonary TB, they were more likely to represent intracerebral tuberculomas (figure 3). The patient was transferred to the Department of Otorhinolaryngology for mastoidectomy, and a sample from the mastoid tissue and middle ear was submitted for microbiological testing. After the operation, he was transferred to the Department of Infectious Diseases. Here we performed a lumbar puncture displaying normal protein value and lack of pleocytosis, suggesting intracerebral tuberculoma without TB-meningitis. Given the isolation of *P. jirovecii* from the patient's lungs, an HIV test was administered and returned negative. We submitted urine and faeces samples as well as histological samples of the removed right testicle for microbiological testing. When all samples returned positive for *M. tuberculosis* DNA, it became clear that the symptom complex which had seemed to represent progressing, non-responsive multiorgan SA was actually a case of disseminated TB.

DIFFERENTIAL DIAGNOSIS

The patient's disease pattern was deemed fully compatible with multiorgan SA by several specialists based on clinical as well as radiological and histological information: HRCT scan showing micronodular changes and consolidated infiltrations, a

biopsy from the lung showing non-necrotising, granulomatous inflammation and MRI of the cerebrum showing multiple small contrast enhancing elements. SA has also been associated with epididymitis, deep venous thrombosis, pulmonary thromboembolisms, weight loss and elevated inflammation markers as presented in this case. As such SA and TB may have a very similar clinical presentation.

Apart from representing a systemic infection, these phenomena could have constituted disseminated malignancy. In accordance with this theory, the small contrast enhancing elements seen on MRI of the cerebrum had a similar appearance to that of multiple brain metastases.

In the end, the discovery of active TB infection was reached as part of the investigation of a suspected superinfection on top of the multiorgan SA. Hereafter, several organ systems were examined for infection with *M. tuberculosis* at the Department of Infectious Diseases. Detection of the bacterium in the patient's brain, mastoid, urinary and gastrointestinal tract led to the final diagnosis of disseminated TB.

TREATMENT

The *M. tuberculosis* displayed full drug sensitivity, and hence we initiated TB treatment in central nervous system dosage, consisting of:

- ▶ Rimstar (isoniazid 75 mg, rifampicin 150 mg, ethambutol 275 mg and pyrazinamide 400 mg), five tablets per day.
- ▶ Pyridoxin 20 mg per day.
- ▶ Moxifloxacin 400 mg per day was added because MRI showed no signs of meningeal inflammation.

After 2 months, continuation phase of treatment consisted of:

- ▶ Isoniazid 600 mg per day.*
- ▶ Rifampicin 750 mg per day.
- ▶ Moxifloxacin 400 mg per day.

Treatment will continue for at least 9 months from initiation date. Daily administration of prednisolone was continued to limit cerebral oedema around the tuberculomas, but with gradually decreased dosage.

Detection of *P. jirovecii* in BAL fluid together with the clinical presentation called for addition of:

- ▶ Sulfamethoxazol 400 mg per day.
- ▶ Trimetoprim 80 mg per day.

*Standard dosage of isoniazid is 300 mg per day. Our patient had a low plasma concentration of isoniazid, and therefore dosage was balanced according to the plasma concentration. This led to an increase of the daily dosage to 600 mg.

OUTCOME AND FOLLOW-UP

At the time of writing this case report, 2 months have passed since the patient was diagnosed with TB. His condition gradually improved over the first 2 weeks of treatment, after which he was discharged from the Department of Infectious Diseases. Two months after diagnosis, the patient was seen in our outpatient clinic, where he reported continuing inadequate lung function and reduced hearing on the operated left ear. X-ray of the thorax showed regression of micronodular changes and infiltrations. Biochemistry revealed steadily decreasing inflammatory markers (C reactive protein and erythrocyte sedimentation rate). We will continue to follow the patient regularly in our outpatient clinic.

DISCUSSION

An important learning point of this case stems from the seemingly identical manifestations of the disseminated TB disease with those of multiorgan SA. Both are multisystemic, granulomatous

diseases, and both can be lethal if appropriate treatment is not initiated in time. Distinguishing between the two disease entities can be immensely challenging as they share both clinical, radiological and histological similarities.¹ Most often, TB causes caseous necrosis while SA granuloma are non-necrotizing, but there are exceptions where one mimics the other.⁶ The diseases have different aetiologies, however, and treatment strategies differ significantly. In both cases, clinical manifestations are the result of T-cell stimulation and secretion of various cytokines, leading to granulomatous inflammation. In SA the aetiology is non-infectious, although still not fully understood. The cornerstone in multiorgan SA treatment is immunosuppression with high-dose corticosteroids.⁷ In TB, however, the immune response is crucial in the control of infection with *M. tuberculosis*. Therefore, immunosuppressive therapy without antibiotics is inappropriate during infection with TB,⁵ which was confirmed by the widespread dissemination of the infection during SA treatment in the case of our patient. Based on the continuous and rather drastic deterioration of lung function despite what was thought to be appropriate treatment, testing for active TB could have been done earlier in the process, illustrating the importance of staying critical towards one's tentative diagnosis. The recurring thromboembolic events could have also contributed to raising suspicion of generalised infection.

Debut of TB in the genitourinary tract (GUTB) is rare, especially in developed countries. It is however the second most common extrapulmonary manifestation of TB.⁸ The symptoms can mimic epididymo-orchitis as well as testicular cancer. Surgical intervention is avoidable if diagnosed in time, since GUTB responds well to standard TB treatment.⁹ This fits well with the regression of testicular symptoms from the remaining left testicle after initiation of treatment in our case.

In retrospect, GUTB could have been suspected when the pathology examination revealed chronic inflammation with focal necrotic areas of the surgically removed right testicle.

TB-incidence in Denmark is low: a total of 297 cases were reported in 2018.³ In more than 61% of cases, the patients were immigrants from countries with a high TB incidence.¹⁰ Other high-incidence groups are the elderly Danish population and socially vulnerable individuals such as the homeless and alcohol or drug abusers.¹¹ Our patient does not fit into any of the mentioned categories. He is a public employee at the local water department, and he has never smoked. Additionally, he has received the BCG-vaccine as a child, further decreasing the suspicion of TB. He has however been travelling to TB-endemic countries, most recently 10 years ago. It seems likely that he acquired a latent TB-infection during his travels. Thus, clinicians in low-incidence countries must maintain a certain index of suspicion regarding TB-infection, even if a patient displays no

Learning points

- ▶ Disseminated tuberculosis (TB) can mimic multiorgan sarcoidosis (SA).
- ▶ Early distinguishing between TB and SA is important for reducing mortality.
- ▶ Screening for TB before initiation of immunosuppressive SA therapy should be considered, even if there is no suspicion of exposure to *M. tuberculosis*.
- ▶ Genitourinary TB should be suspected when pathological examination of testis shows focal necrosis.

immediate exposure and does not belong to a high-risk group within the population.

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