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Case report

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Adopted Korean woman with symptoms of cystitis – Delayed diagnosis of tuberculosis leading to disseminated disease

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Abstract

We report a rare case of miliary tuberculosis (TB) in an adopted woman that developed following delayed diagnosis of presumed urogenital TB. The patient had a two year history of urological symptoms, diagnosed as interstitial cystitis and treated with cyclosporine. At admission, she presented with symptoms of pyelonephritis. Neck stiffness led to lumbar puncture that showed pleocytosis with lymphocytic predominance, high protein and low glucose levels, suggestive of TB meningitis. Computed tomography and magnetic resonance imaging scans showed nodular lung changes, lumbar spine destructive lesions, a unilateral kidney abscess and a parietal lobe tuberculoma. Urine and cerebrospinal fluids were positive for TB by polymerase chain reaction (PCR) and culture. The patient developed complications in the form of hydrocephalus. She was treated with a ventriculoperitoneal shunt and four drug anti-tuberculosis therapy. She was discharged to neurorehabilitation on continued anti-tuberculosis treatment, developing longer term sequelae in the form of severe cognitive disabilities. This case emphasizes the importance of continuing to include TB in the differential diagnosis of a variety of diseases, particularly in patients at possible increased risk of infection, and highlights the potentially serious consequences of delayed or missed TB diagnosis.

Keywords: miliary tuberculosis; interstitial cystitis; urogenital tuberculosis; tuberculoma; meningitis; non-endemic

Introduction

Infection with *Mycobacterium tuberculosis* is a rare disease in Denmark with an incidence of 6.7/100.000, the majority of patients being born outside Denmark in countries with high rates of endemic infection [1]. Spread by airborne transmission, the initial infection resolves in most individuals. However, latent tuberculosis can reactivate in up to 5% of healthy individuals, even after an interval of several decades [2]. The mechanisms of reactivation are unknown, but immunosuppressant drug therapy increases reactivation risk. Reactivation can present as extra-pulmonary TB [3], urogenital TB being second only to lymph node infection in frequency [2]. In contrast, only 50 cases of TB meningitis have been reported in Denmark in the period 2001-2008 and only a few of these had an additional site of extra-pulmonary TB other than meningeal [1].

With this case we want to draw attention to the serious consequences of delayed diagnosis and treatment of TB. We wish to raise awareness that the infection can mimic a variety of disease entities and that the clinician ought, therefore, be suspicious of TB in patients with known risk factors (e.g. adopted individuals, refugees and immigrants from high-endemic countries, and patients receiving immunosuppressives). Since the 1980s, the number of immigrants to Denmark from non-western countries has increased fivefold. Immigrants and their descendants account for 5.8% and 2.5%, respectively, of the Danish population in 2016 [4], making this case highly relevant.

Case report

In August 2014, a 40-year-old woman was admitted to our medical department with a two-week history of fever, headache, unilateral flank pain, dizziness and night sweats. She had been adopted from Korea and came to Denmark at the age of three years. Apart from an earlier diagnosis of uterine cervical dysplasia, she had been well until being referred to the Department of Urology in the summer of 2012 for investigation of suspected cancer, having

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had frequent, recurring voiding symptoms, unilateral flank pain, sterile pyuria and episodic fever. At that time, computed tomography (CT) urography showed thickening of the bladder wall, the right renal pelvis and proximal ureter with renal caliectasis, a low attenuated process with multiple calcifications in the parenchyma, and enlarged lymph nodes in relation to the right renal artery (Figure 1). Ureteroscopy and cystoscopy were reported as showing multiple bladder ulcers (Hunner's ulcers), signs of chronic inflammation and renal papillary necrosis. Urine cytology showed inflammation with many granulocytes, but no cancer cells. Biopsies from the necrotic papillae and the bladder revealed pronounced mucosal inflammation dominated by lymphocytes. In addition, increased numbers of mast cells were found in the underlying tissues (confirmed by immunohistochemical staining with mast cell marker CD117) and the patient was diagnosed with interstitial cystitis (IC) with Hunner's ulcers/bladder pain syndrome (BPS).

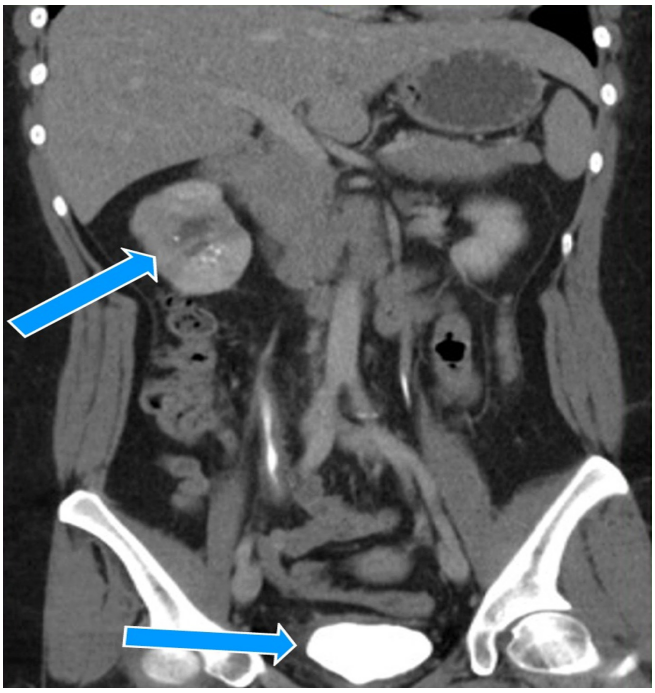

Figure 1 Contrast enhanced CT urography scan, July 2012, showing a thickened bladder wall on the right side, a thickened right ureter and low enhancement parenchymal changes in the right kidney, which might represent the early changes seen in renal tuberculosis, so-called multiple papillary necrosis resulting in uneven caliectasis.

From July 2012 to October 2013, the patient was treated with hydrodistension and electrocoagulation, ranitidine, mirabegron, prophylactic trimethoprim, intravesical administration of chondroitin sulphate (0.2% and 2%), and electromotive drug administration with lidocaine and solu-medrol. In spite of this, the patient's symptoms became more severe, with increasing bladder pain and increasingly frequent micturation (up to 40 times/day).

During this period, the patient had multiple hospitalizations at the Department of Urology for what was interpreted as urinary tract infection. Notably, urine cultures were consistently negative for bacterial growth, with one exception when significant numbers of group B streptococcus were cultured. Furthermore, she had a persistently raised C-reactive protein (CRP) at around 25-143 mg/L (normal < 8 mg/L) with leukocytes within the normal range.

In January 2014, the patient started treatment with cyclosporine (50 mg × 2) on suspicion of unmanageable IC/PBS resistant to prior drug therapy. In April 2014, she discontinued the treatment on her own initiative, because of progression of symptoms in the form of severe lower back pain and increasing abdominal pain. Because of this progression, a contrast enhanced CT scan was performed. This showed wall thickening of the right renal pelvis and ureter, one enlarged retroperitoneal lymph node, and non-specific infiltrative changes in the lungs, including a few 5-6 mm nodules together with a single 9 mm round process in the lung parenchyma. Biopsy from the retroperitoneal lymph node was unsuccessful. The patient was referred to the Department of Pulmonary Medicine who recommended a new CT scan 3 months later. A supplementary renography was performed which showed only 14% renal capacity remaining in the right kidney and a pig-tail stent was temporarily inserted.

Because of the patient's continued fever, the Department of Infectious Diseases was consulted. Fever, lung nodules and acute right renal failure were felt to be suspicious for vasculitis. However, there was no other evidence of vasculitis, the patient having negative anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA) and absent urine cylinders.

At the time of admission to our medical department in August 2014, the patient had fever (38.6°C), urine with pus cell count 15 leucocytes/μL, protein 1 g/L, 200 erythrocytes/μL, and no nitrite. CRP was 18 mg/L (normal < 8 mg/L), with slightly elevated neutrophil leukocytes 8×10^9/L (normal 2×10^9–7×10^9/L) and hyponatremia 132 mmol/L (normal 137-145 mmol/L). X-ray of the chest showed progression of the pulmonary nodular changes found five months earlier (Figure 2). Because of the long medical history with no clear diagnosis, the patient was thoroughly investigated for granulomatous disease and immunosuppression with p-interleukin-2-receptor, p-HIV 1+2 antigen/antibody, immunoglobulins IgA, IgM, IgG and IgG subclasses, ANA, ANCA, CD4 and CD8 cell counts (the above-mentioned all being negative or within the normal range), interferon-gamma release assay and a contrast enhanced CT scan of thorax, abdomen and paranasal sinuses was booked. On the second day of admission the patient developed fever (39.3°C) and severe headache in spite of Piperacillin/Tazobactam treatment. Objectively, she had moderate neck stiffness. A lumbar puncture was performed on suspicion of meningitis. The cerebrospinal fluid (CSF) was colourless. Total white cell count was 403×10^6/L (normal < 5×10^6/L), consisting of mononuclear leukocytes 238×10^6/L (normal < 5×10^6/L) and polynuclear leukocytes 165×10^6/L (normal < 1×10^6/L). CSF-glucose was 1.3 mmol/L (normal 2.5-4.5 mmol/L), p-glucose 9.3 mmol/L (normal 4.2-7.8 mmol/L), CSF-protein 1.45 g/L (normal 0.15 - 0.5 g/L), CSF-erythrocytes 1000×10^6/L (normal 0). On suspicion of meningoencephalitis, treatment with benzylpenicilline, cephalosporine and aciclovir was started

according to Danish guidelines. Because of the patient's poor condition, acute whole-body CT scans and magnetic resonance imaging (MRI) of the brain were performed in order to help differentiate between infection, cancer and autoimmune disease.

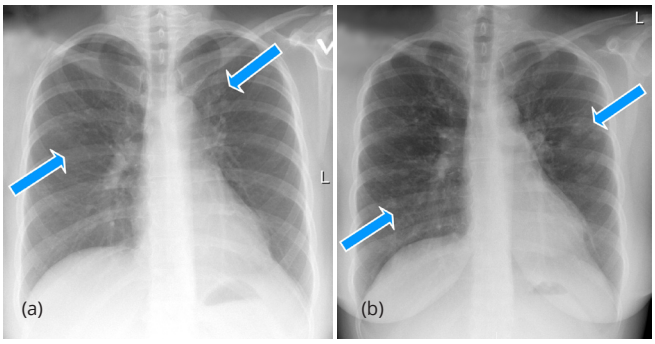

Figure 2 (a) Chest X-ray demonstrates non-specific patchy reticulonodular opacities at the perihilar regions without any cavitations or calcifications; (b) Progression of bilateral central opacities with multiple ill-defined opacities with cavitations.

The MRI showed a 10×9 mm high-signal lesion during contrast in the right parietal lobe with peripheral oedema and thickening of the meninges, with no signs of vasculitis (Figure 3). CT scan of the lungs showed progression in the multiple 1-3 mm nodules (suspect for miliary deposits) and tree-in-bud appearance in both lungs, representing endobronchial spread of infection that can be caused by *M. tuberculosis* in pulmonary TB (Figure 4), and bone destruction was detected in L1, L2 and L3 (Figure 5). Furthermore, a 23 mm centrally necrotic abscess was detected in the right renal medulla (Figure 6). In spite of these findings, the patient was still radiologically suspected of having disseminated cancer. However, at this point the case was discussed with an infectious diseases specialist. The lumbar puncture findings and the patient's Korean origin led to the suspicion of miliary TB. Acute investigations of the CSF, urine and blood for TB by PCR were performed. The interferon-gamma release assay was positive and *M. tuberculosis* complex was detected by PCR and acid-fast bacilli were visible by direct microscopy in the CSF and urine. Urine cultures for *M. tuberculosis* were positive with no sign of resistance against standard anti-TB therapy. As soon as TB was diagnosed, the patient was isolated and transferred to the Department of Infectious Diseases, where she received four drug anti-TB treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, in combination with dexamethasone.

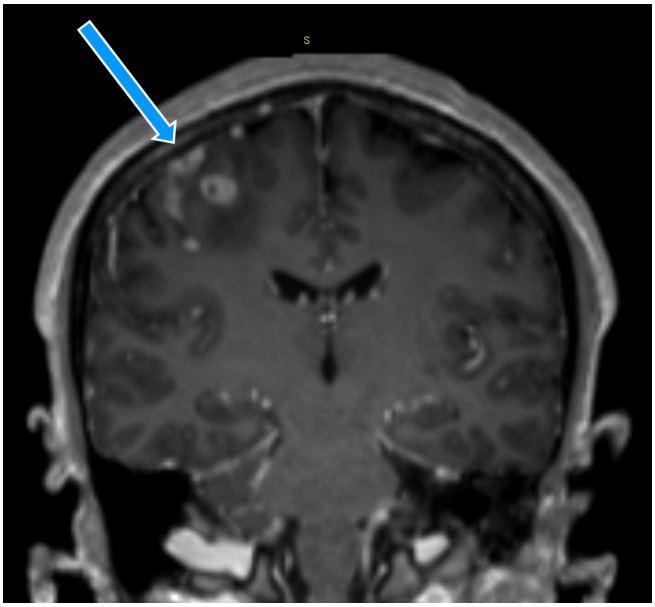

Figure 3 Cerebral MRI scan, August 2014, with infusion of a paramagnetic contrast agent demonstrates an intracerebral high-signal lesion during contrast in the right cerebral hemisphere with peritumoral edema and meningeal spread. The lesion is characterized by a small necrotic central part and is most likely a tuberculoma.

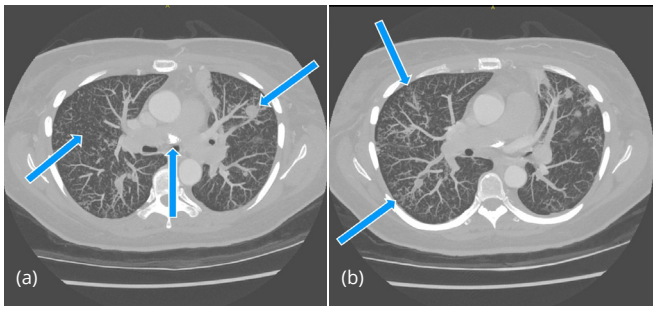

Figure 4 (a) Contrast enhanced CT scan of the thoracic, abdominal and pelvic regions, August 2014, showing the tree-in-bud appearance in both lungs, representing presumed endobronchial spread of infection that can be caused by *M. tuberculosis* in pulmonary TB. Miliary deposits are seen, with multiple 1-3 mm nodules which are uniform in size and uniformly distributed. In both lungs, there are localised tuberculomas without calcification. Note the calcified lymph node located caudally to the carina, suggestive of previous TB (latent) infection (b).

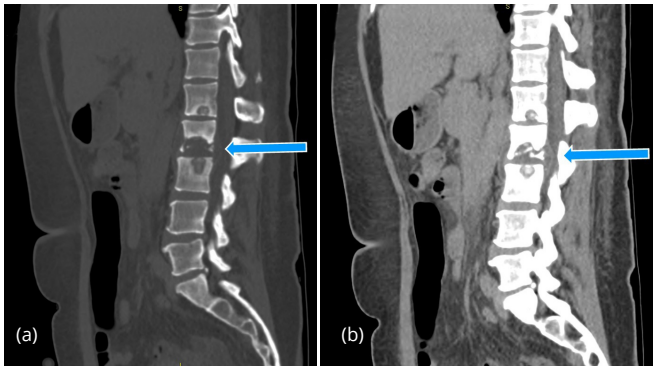

Figure 5 (a) Bone setting: Contrast enhanced CT scan of the thoracic, abdominal and pelvic regions, August 2014, with a bone algorithm and sagittal reconstruction of the lumbar spine shows destruction of the L1, L2 and L3 centered on the intervertebral discs, caused by tuberculous vertebral body osteomyelitis; (b) Soft window setting: An extensive paraspinal soft tissue mass is present prevertebral as well as epidural, causing a relative spinal and left foraminal stenosis.

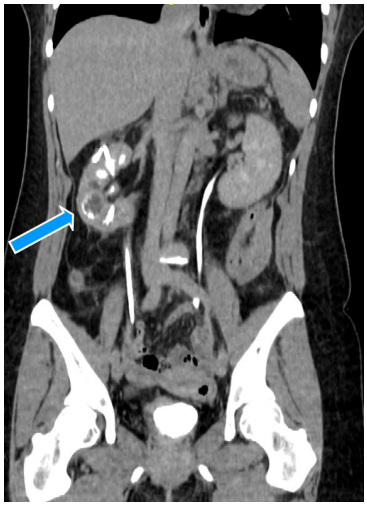

Figure 6 Contrast enhanced CT scan of the thoracic, abdominal and pelvic regions, August 2014, showing end-stage right sided kidney disease with an only 10% remaining function, a permanent pig-tail stent displaced cortically, and a parenchymal delayed contrast wash-out with some partly calcified abscesses/ tuberculomas.

Within the first 24 h of anti-TB treatment, the patient developed complications in the form of normal pressure hydrocephalus and consequently had a ventricular-peritoneal shunt implanted. She was discharged after 46 days of hospitalization with an expected treatment time with anti-TB therapy of 12 months. Her main sequelae at discharge were severe lack of memory and lack of initiative, together with difficulty in concentration. Therefore, she was discharged to a neurorehabilitation centre.

Discussion

This is a rare case of miliary TB in a non-endemic country, presumed to result from reactivation of a more than 37-year-old latent TB infection. The case shows the serious consequences of delayed diagnosis. The initial CT urography of the kidneys with unilateral low-attenuation parenchymal lesions, mural thickening, calcifications, papillary necrosis and calyceal dilatations are known radiologically to be TB associated findings [2, 5] with a 91.4% sensitivity (although specificity is not very high). Over 50% of urogenital TB cases have renal calcifications on CT scans, whereas "moth-eaten" papillae can be an early finding in renal TB [5, 6]. Culture of the urine for TB, the diagnostic gold standard, shows 96.7% specificity, but widely varying sensitivity (10.7% to 90%) [2, 7]. In the present case, superficial biopsies from the bladder wall were without granulomas. This is consistent with the poor sensitivity of bladder biopsies for TB (18.5% to 52% sensitivity) [1]. Furthermore, no granulomas were found in the initial biopsy from the necrotic renal papillae. This may be sampling artefact, since this biopsy was small, but it may also be explained by the fact that granulomas tend to form in the renal cortex and not the renal medulla in the early stages of renal TB [5, 6]. Because there was no initial suspicion of TB, and because only non-specific chronic inflammation was found in the renal papilla and bladder biopsies, these were not stained with Ziehl-Neelsen stains and no urine was cultured in Lowenstein-Jensen medium. This, in spite of the fact that at the time of diagnosing this patient with IC/BPS, the European Society for the Study of Interstitial Cystitis had stated in their 2008 consensus diagnosis of IC/BPS that confusable diseases causing symptoms such as frequent voiding/pelvic pain included TB, and that this infection should be excluded before making a diagnosis of IC [8, 9]. This guideline is particularly relevant in high risk patients.

To our knowledge, only a few similar cases with both urogenital and meningeal TB have been published [9-12]. In one of these cases, the diagnosis of TB was also delayed due to an initial diagnosis of IC [9]. Since our patient had no relevant travel history, we assume that she experienced a reactivation of an almost 37-year-old TB infection, initially acquired within her first three years of life in the Republic of Korea, a country in which the present TB incidence rate is around 80/100.000 according to the WHO [13].

With the benefit of hindsight, the patient presumably had a urogenital TB focus that led to miliary TB. Treatment with cyclosporine probably accelerated the course of the disease, since this was associated with immediate worsening of symptoms. It is well-known that immunosuppressive drugs, such as cyclosporine, can cause reactivation of a latent TB infection, or make the patient more susceptible to a primary TB infection [3, 14]. Cyclosporine is an established treatment for IC [15], but this case emphasizes the importance of TB screening before initiation of immunosuppressant therapy in patients with IC, as suggested by the European Society for the Study of Interstitial Cystitis [8]. The majority of medical departments in Denmark prescribing immunosuppressive drugs regularly perform TB screening as a routine precaution, but the less familiar the clinician is with immunosuppressant drugs, the more likely TB screening is to be forgotten. This case emphasizes the importance of TB screening prior to initiation of immunosuppressive therapy, especially in patients at high risk of infection.

In Denmark, the international adoption rate is around 400 children/year; there is no data on the prevalence of TB in these children. However, studies from the USA show that 3% - 12% of internationally adopted children have either active or latent TB on arrival [16, 17]. Contact screening is an important preventive measure that has not always been fully implemented in Denmark. Therefore, also second-generation descendants of immigrants may be at risk of infection with TB. Of relevance, the National Hospital of Denmark opened a specialized department for adopted children in 2009 implementing a systematic screening programme, including screening for TB.

TB incidence rates in Denmark are likely to increase in the future, because of the present rise in the numbers of refugees from high-endemic countries. This emphasizes the need for precautionary measures such as screening, Greenland, with its close relation to Denmark, being a painful reminder of the consequences of not controlling TB. In Denmark, every refugee should by law be offered a medical examination within three months of arrival [18]. However, unlike in other northern European countries, TB screening is not mandatory in order to be granted a residence permit, with the result that some TB-infected patients will be missed. Furthermore, prior experience shows that compliance to a systematic TB control programme is difficult for refugees, suggesting that TB incidence rates may increase over the coming years in Denmark.

Conclusion

Miliary TB only affects a handful of people each year in non-endemic countries. However, there should be a high index of suspicion for this infection in the differential diagnosis of many diseases, since patients at high risk for TB form an increasing proportion of the population in low-endemic countries, and the consequences of delayed diagnosis, as exemplified in this case report, may be severe.

Ethics, consent and permissions

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: For this type of study, formal consent from the local ethical committee is not required. However, the events were reported to the Danish Patient Safety Database.

Informed consent: Informed consent was obtained.

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