Other full case

PCR use in miliary tuberculosis presenting with acute respiratory distress syndrome

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Summary

A 30-year-old pregnant woman admitted to the hospital for rapidly progressive dyspnoea, non-productive cough and altered general status evolving over 1-month period. Her vital signs showed a low blood pressure 90/60 mm Hg, pulse rate 100 beats/min, respiratory rate 32 breaths/min and oxygen saturation on room air of 88%. Laboratory findings showed haemoglobin 9.7 g/dl, white blood cells 15 000/mm³ (neutrophils 82%), C reactive protein 74 mg/l, alkaline phosphatase 320 U/l, alanine aminotransferase 62 IU/l, aspartate aminotransferase 120 IU/l, γ glutamyl transpeptidase 125 U/l; brain natriuretic peptide 25.4 pg/ml, procalcitonine >2, lactate dehydrogenase 1618 U/l. Chest radiographics showed diffuse bilateral micronodular pulmonary infiltrates and CT of the chest confirmed 1–3 mm diffuse bilateral micronodular infiltrates with ground glass opacities. Complete investigation including bronchoalveolar lavage (BAL) for any viral, bacteriologic, acid-fast bacilli and full serum antibodies panel were all negative. DNA amplification for mycobacterium using PCR on the BAL rapidly rectified the diagnosis of tuberculosis.

BACKGROUND

Fulminant miliary tuberculosis (TB) complicated with acute respiratory distress syndrome (ARDS) is relatively rare and the prognosis is extremely poor. Laboratory facilities to confirm the disease especially DNA amplification techniques using PCR may herald a prompt and accurate management.

CASE PRESENTATION

A 30-year-old woman on 16-weeks gestation with twins by in vitro fecundation presented to our hospital for a rapidly progressive dyspnoea, non-productive cough and altered general status evolving over a period 1 month. Four days before her admission, she started a 38.5°C fever with chills, night sweats, headache and painful uterine cramps/contractions and bleeding.

On admission, she seemed profoundly ill. Her vital signs showed a low blood pressure 90/60 mm Hg, pulse rate 100 beats/min, respiratory rate 32 breaths/min and oxygen saturation on room air of 88%. Chest examination revealed respiratory distress with high shallow breathing and bilateral diffuse pulmonary crackles. Her obstetrical examination showed an incomplete dilated cervix confirming an inevitable spontaneous abortion.

INVESTIGATIONS

Laboratory findings showed haemoglobin 9.7 g/dl, white blood cells (WBC) 15 000/mm³ (neutrophils 82%, lymphocytes 10%); platelet count 321 000/mm³, C reactive protein 74 mg/l, creatinine 52 micromol/l, alkaline phosphatase 320 U/l, alanine aminotransferase 62 IU/l, aspartate aminotransferase 120 IU/l, γ glutamyl transpeptidase 125 U/l, brain natriuretic peptide 25.4 pg/ml, procalcitonine >2, lactate dehydrogenase 1618 U/l. Blood gases on

admission showed marked hypoxemia with pH 7.45, PCO₂ 26 mm Hg, PO₂ 95 mm Hg on non-rebreather mask with 15 l/min of oxygen.

Chest radiograph showed diffuse bilateral micronodular pulmonary infiltrates and CT of the chest confirmed 1–3 mm diffuse micronodular infiltrates with ground glass opacities at both inferior lobes as well as in the middle lobe and the lingual with alveolar infiltrate containing microcalcifications in the right apex. A diagnosis of ARDS is evoked and patient was admitted to the intensive care unit.

DIFFERENTIAL DIAGNOSIS

A complete investigation to determine the aetiology of the ARDS was performed. Repeated blood and sputum cultures and urinary antigen for Legionella were negative; bacterial and viral serology antibody titres for Chlamydia, Mycoplasma, Cytomegalovirus, Epstein–Barr virus, Hepatitis B and C virus, HIV1-2 were all found to be negative; PPD skin test and repeated sputum and gastric Ziehl–Neelsen colouration were negative. Immunologic studies including antinuclear antibodies, rheumatoid factor, anti-dsDNA, perinuclear antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic ANCA, C3 and C4 were all found to be negative.

A bronchoscopy with bronchoalveolar lavage (BAL) was then performed; it showed a lymphocytic alveolitis with 1200 red blood cells (RBCs) and 330 WBC (80% lymphocytes). Flux cytometry results showed 50% lymphocytes (CD4/CD8 0.705), 36% macrophages (CD14 CD1a). No acid-fast bacilli (AFB) were visualised and usual bacterial culture was negative. DNA amplification for *Mycobacterium tuberculosis* using PCR was performed. MRI for the brain and lumbar puncture with PCR for TB was unremarkable.

TB was confirmed with a positive result of PCR on the BAL and on bronchial aspiration specimens. The histologic examination of the expelled tissue confirmed products of conception without signs of TB.

TREATMENT

She was promptly started on a rapid volume expansion therapy with high level of oxygen using non-rebreathing mask (15 l/min) and on empiric antibiotic (ceftriazone 2 g intravenous/24 h and azomycine 500 mg intravenous/24 h) and an aggressive hormonal supplements trying to avoid fetal demise with hydroxyprogesterone hexanoate and dydrogesterone.

After the confirmation of TB, the patient was started on a quadritherapy regimen and moderate dose of dexamethasone 2 mg intravenous/12 h, then shifted to prednisolone 10 mg per day.

OUTCOME AND FOLLOW-UP

On the 3rd day, the entire contents of the uterus were expelled resulting in a complete spontaneous abortion.

After the initiation of the quadritherapy regimen and corticosteroids, on the 9th day the patient was transferred to the floor after improvement of her respiratory failure needs for oxygen (6 l/min on nasal cannula). She was discharged from the hospital 1 week later without significant dyspnoea, cough or fever. She was instructed to continue her anti-TB therapy for 12 months and to adhere to her follow-up visits. After 7 weeks, Lowenstein culture confirmed typical *M tuberculosis*.

DISCUSSION

Miliary TB (MTB), now used to denote all forms of progressive, widely disseminated hematogenous TB, can have a highly variable clinical presentation.¹⁻⁴ MTB poses a particular diagnostic challenge for clinicians. Multiple factors contribute to the omission of a rapid diagnosis and influence the treatment outcome. The obscure late non-specific miliary pattern presentation and the relatively insensitive and slow bacteriological methods for detecting *Mycobacterium* accounts often for the missed diagnosis.⁵⁻⁷ When it is suspected it is important to carry out the complete range of tests (Ziehl-Neelsen microscopy, PCR, Lowenstein cultivation) for a prompt diagnosis and to start therapy immediately.⁸⁻⁹ In one review, 18% of cases with MTB were diagnosed postmortem, compared with 4.8% among those with pulmonary TB.¹⁰

MTB is an uncommon, but important treatable cause of ARDS. It was estimated that 1-2% of cases of ARDS were associated with disseminated TB.¹¹ Moreover, the heterogeneity of populations meeting criteria for ARDS may explain in part why no specific treatment has yet been shown to decrease mortality. In an autopsy study of 69 ARDS patients, only 50% had a typical diffuse alveolar damage (DAD).¹² Pinheiro *et al* reported recently that of 22 patients diagnosed of ARDS, only 10 (45%) met the American-European Consensus Conference criteria, and 7 (32%) met the histopathological criteria for DAD.¹³

Predictors of ARDS development secondary to TB are MTB, disease course more than 1 month before treatment, lymphocyte count less than 1625/ml and alanine transaminase > 100 UI/ml.¹⁴ Isobe *et al* reported that pregnancy may have been the risk for the development of MTB complicated with ARDS.¹⁵

ARDS caused by miliary TB is associated with a high death rate varying between studies between 23.5% and more than 60%.¹⁶⁻¹⁷ Delayed treatment for 1 month increases the mortality by more than threefold.¹⁷

Meningeal involvement is evident in postmortem in up to 54% of cases of fatal miliary TB.¹⁸ Although our patient had a severe headache, neither the brain MRI nor the lumbar puncture were conclusive with negative cerebrospinal fluid culture and PCR for TB.

In patients with ARDS rapid course of disease necessitates aggressive diagnostic investigation including extra pulmonary biopsies notably of bone marrow and liver. However, the liver and bone marrow biopsies were not performed in our case because the liver enzyme profile was in the upper normal limit and no alteration in peripheral blood results (WBC, RBC and platelets) was detected.

Several laboratory abnormalities with isolation of *M tuberculosis* from sputum, body fluids or tissue biopsy specimens are useful for the confirmation of diagnosis. Nucleic acid amplification (NAA) using PCR are useful methods to determine a fast and accurate diagnosis in pulmonary TB and extrapulmonary disease.¹⁹ Protocols for respiratory isolation based upon the first sputum was illustrated in a prospective study including 679 patients.²⁰ All 35 AFB smear-positive patients had positive NAA tests. Among 46 patients with culture-positive TB, more cases were identified by NAA than by serial AFB smears (87% vs 76%, respectively). In a low prevalence population, sensitivity and specificity of PCR compared with those of culture were 68% and 97.4%, respectively. For culture-positive, smear-negative samples, the sensitivity of the amplicor PCR was 46%.⁸ PCR in aspirates of bone marrow was demonstrated to be a useful diagnostic assay in cases of MTB, mainly when bacteriological results are negative in 16.6%.⁶ Nojima *et al* reported recently the case of a 86-year-old woman who had MTB complicated by ARDS in which PCR was positive but in AFB were also detected in urine and sputum.¹⁹ Our case is a case of ARDS with MTB diagnosed by PCR with multiple negative smear sputum and BAL. The pure hematogenous spread of the AFB in MTB could explain the negative bacteriologic studies. In addition, the detection of *M tuberculosis* DNA in peripheral blood mononuclear cells was positive in 100% of a small number of patients with disseminated disease.²¹

Diagnosis of ARDS aetiology poses a particular challenge for clinicians. The omission of TB from the differential diagnosis of patients with ARDS and the relatively insensitive bacteriological methods for detecting *M tuberculosis* add to the complexity of the problem. All laboratory facilities to confirm the disease especially DNA amplification techniques using PCR may herald in the prompt and accurate management of MTB and ARDS TB.

Learning points

- Diagnosis of ARDS aetiology poses a particular challenge for clinicians.
- The omission of TB from the differential diagnosis of patients with ARDS and the relatively insensitive bacteriological methods for detecting *M tuberculosis* add to the complexity of the problem.
- DNA amplification techniques using PCR may herald the prompt and accurate management of MTB and ARDS TB.

Competing interests None.

Patient consent Obtained.

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