PERINATAL TUBERCULOSIS WITH MILLIARY PATTERN IN INFANT AGED 28 DAYS

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ABSTRACT

Perinatal tuberculosis (TB) was a very rare case. Its clinical manifestations could mimic bacterial infection. The clinical course was often fulminant and characterized by dissemination and meningitis. Its mortality was very high, could achieve 100% in untreated patient. We reported a case of infant aged 28 days admitted with breathlessness, fever, and poor feeding. Physical examination showed breathlessness, pale, lethargy, and hepatomegaly. Chest radiograph showed a feature of milliary pattern with fine tubercles in both lung, supported with positive result on gastric aspirates for acid fast bacilli 3 days respectively. Gastric aspirate culture for *Mycobacterium tuberculosis* showed positive result. Patient then diagnosed with perinatal TB with milliary pattern. This condition was accompanied with severe sepsis and meningitis. Four TB regimens (isoniazid, rifampisin, pirazinamide, and ethambutol), corticosteroid, antibiotics were given. The patient was eventually died after receiving TB therapy for 13 days. **[MEDICINA 2014;45:208-212].**

Keywords: *tuberculosis, milliary, perinatal*

TUBERKULOSIS PERINATAL DENGAN GAMBARAN MILIER PADA BAYI BERUSIA 28 HARI

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ABSTRAK

Tuberkulosis (TB) perinatal merupakan suatu penyakit yang sangat jarang dijumpai. Manifestasi klinis dapat menyerupai infeksi bakteri. Perjalanan penyakitnya seringkali berat dengan karakteristik diseminata dan meningitis. Angka kematian sangat tinggi, dapat mencapai 100% pada pasien yang tidak mendapat pengobatan. Kami melaporkan sebuah kasus bayi berusia 28 hari dengan sesak napas, demam, dan malas minum. Pemeriksaan fisik menunjukkan sesak napas, pucat, letargi, dan hepatomegali. Foto roentgen dada menunjukkan gambaran milier dengan tuberkel halus di kedua paru, didukung dengan hasil positif pada pemeriksaan basil tahan asam di cairan lambung 3 hari berturut-turut. Biakan cairan lambung untuk *Mycobacterium tuberculosis* menunjukkan hasil positif. Pasien kemudian didiagnosis dengan TB perinatal dengan gambaran milier. Keadaan tersebut disertai dengan sepsis berat dan meningitis. Empat regimen TB (isoniazid, rifampisin, pirazinamid, dan etambutol), kortikosteroid, serta antibiotik diberikan pada pasien. Pasien meninggal setelah mendapat pengobatan TB selama 13 hari. **[MEDICINA 2014;45:208-212].**

Kata kunci: *tuberkulosis, milier, perinatal*

INTRODUCTION

Tuberculosis (TB) has increased rapidly over the past three decades worldwide,[1] particularly in HIV endemic and impoverished areas in Africa and Asia.[2] Perinatal TB itself is a very rare condition.[3] Only 300 cases were reported in the literature until 1989. Subsequently, 58 cases were reviewed in 1994, and from 2001 to December 2005, 18 more cases have been reported.[3,4]

The clinical features of perinatal TB can be subtle and difficult to differentiate from other neonatal infections. Therefore the diagnosis of perinatal TB is frequently delayed.[4,5] Its mortality is high, varying between 2 and 60% depending on delay to presentation and other factors, such as prematurity and coinfection with HIV.[1] Paediatricians should always be involved in the management of children at risk of or suspected to have neonatal TB.[4,5]

We report a case of infant aged 28 days with perinatal TB accompanied with sepsis and meningitis. The aim of this report is in order to know clinical features, diagnosis, and management of perinatal TB itself.

CASE ILLUSTRATION

Infant aged 28 days was admitted with 3 days history of breathlessness, 5 days history of fever, and 1 day history of poor feeding. The activities were decreased and looked sleepy. The patient has not received BCG immunization yet.

Patient was born in midwife, spontaneously, vigorous, gestational age 38-39 weeks, weighted 2,200 gram, birth length 48 cm, and head circumference 32 cm.

Patient was the first child from the first pregnancy and lived with her both parents. While pregnant, her mother was 18 years old, maternal weight gain was only 4 kg. No history of prolonged fever more than 2 weeks, cough over 3 weeks either accompanied with blood or mucous, cold sweat at night, decrease appetite, and diarrhea. Grandmother died 1 year ago at Sanglah Hospital with pulmonary TB, but hadn't received TB drugs yet.

On physical examination, patient was lethargy, pale, breathlessness. Breath and heart sounds were normal. Hepatomegaly was also found. Further investigation carried out were septic workup, chest radiograph, and lumbal puncture. Chest radiograph revealed a feature of fine tubercles (millier) in both lung, supported diagnosis of milliary TB (**Figure 1**). Cerebrospinal fluid (CSF) macroscopic analysis showed clear CSF and no xantocrom appearance. On microscopic analysis, there was no erythrocytes, glucose 35 mg/dL (comparasion with serum glucose was 30%), protein 153 mg/dL with nonne ++, pandy ++, cell 36 (mono 70%, poly 30%). The patient was later diagnosed with suspect milliary TB with meningitis and suspect late onset neonatal sepsis. Patient then received antibiotics piperacillin tazobactam and amikacin empirically.

On the fifth day care, the condition of patient was deteriorated. Piperacillin tazobactam then replaced into cefoperazone sulbactam. Inotropic was also given due to septic shock. Investigation towards possibility of secondary immunodeficiency traced by Allergy and Immunology Division showed nonreactive result on her mother (serology examination for HIV).

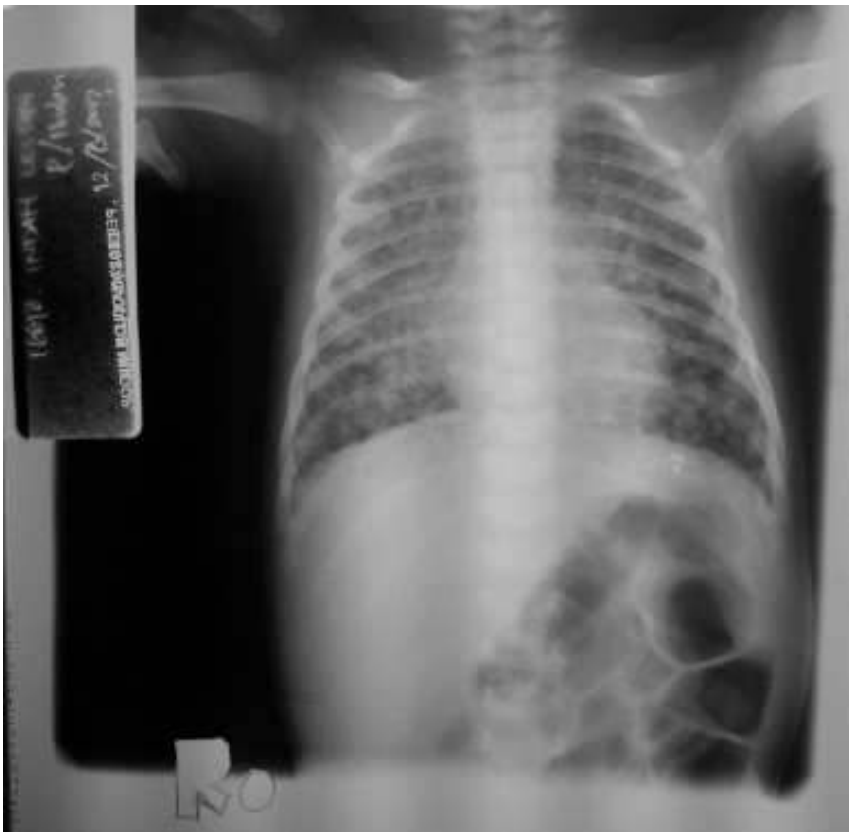

Figure 1. Chest radiograph at the time of patient admitted.

On the eighth day care, 3 days consecutive AFB on gastric aspirates showed result +3 on 1st day, +2 on 2nd day, and negative result on 3rd day. Considering normal liver function, patient was immediately given antituberculosis drugs including isoniazid 10 mg/kg/day, rifampicin 15 mg/kg/day, pirazinamide 30 mg/kg/day, ethambutol 20 mg/kg/day and prednisone 1 mg/kg/day.

There was no organism growth seen in two-sided blood culture, as well as on the result of CSF culture. On the other hand, culture of gastric aspirate revealed growth of *Mycobacterium tuberculosis*. On the abdominal USG, liver was under normal circumstances. On the 19th day of treatment, after the provision of antituberculosis and prednisone for 13 days, the patient's condition was deteriorated. Chest radiograph showed no improvement (**Figure 2**). Patient was eventually died on September 3rd 2013.

At the time of patient treated, her mother was also underwent treatment in Sanglah Hospital with suspect peritonitis. Based on abdominal multislice computed tomography (MSCT) examination, intraabdominal abscess suspicions was detected. Surgical laparotomy emergency was then performed. At the time of laparotomy, intestinal serosa nodule was found. Therefore intestinal TB was suspected. Nodule or infiltrate histopathology examination showed a feature appropriate for supurative acute inflammation. Polymerase chain reaction (PCR) for TB examination on pus showed negative result.

Mother complained bad smelling pus from wound 25 days

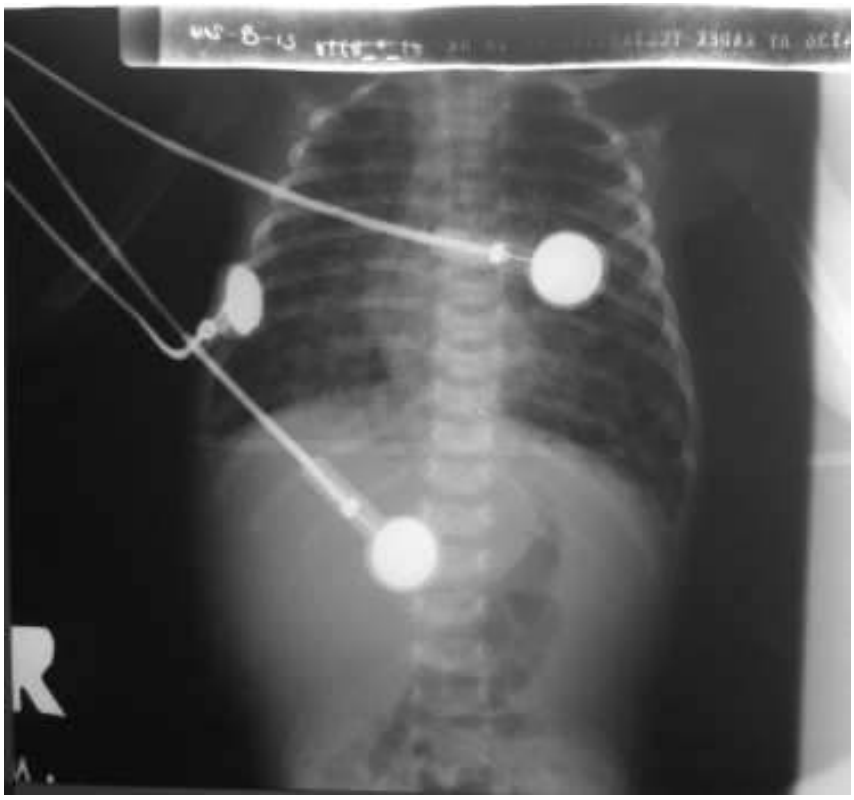

Figure 2. Chest radiograph on September 3rd 2013.

after laparotomy and then treated with enterocutaneous fistel. Chest radiograph showed minimal pleura effusion in right lung suspected with pulmonary TB. Acid fast bacilli smear on pus from wound showed negative result, as well as on AFB smear from sputum 3 days respectively. *Enterococcus sp* and *Candida albicans* were detected on sputum culture. Based on those findings, diagnosis of pulmonary and extrapulmonary TB were excluded. Mother condition was deteriorated. After 26 days of treatment, mother was died due to septic shock.

DISCUSSION

Tuberculosis affected an estimated 8.8 million people and caused 1.4 million deaths globally in 2010, including a half-million women and at least 64,000 children.[2] Tuberculosis among pregnant women is not uncommon, eventhough documented cases of perinatal TB are conspicuous by their rarity. Only 300 cases were reported in the literature till 1989. Subsequently, 58 cases were reviewed in 1994, and from 2001 to December 2005, 18 more cases have been reported.[3] Based on report of WHO in 2010, Indonesia was ranked 4th in the world after India, China, South Africa for its incidence rate with total new cases notified was 296,272 cases in which 28,312 (9.6%) cases were found in children aged 0-14 years and 71,914 (24%) cases were found in women aged 15 years-44 years.[3] In our case, patient was 28 days old. Just as the other countries in the world, epidemiological data regarding perinatal TB in Indonesia was not available yet.

Perinatal TB is the preferred description encompassing TB acquired in utero, intrapartum, or during the early newborn period.[1] There are many routes of transmission for perinatal TB.[6] Distinguishing between the time frames is not crucial, as the presentation, diagnosis, management and prognosis are similar.[1] The only criteria for distinguishing congenital TB from postnatally acquired TB were first proposed by Beitzke in 1935 and revised by Cantwell et al. in 1994. According to the revised criteria, the infant must have proven TB lesions and at least one of the following: lesions present in the first week of life; a primary hepatic complex or caseating hepatic granulomas; TB infection of the placenta or the maternal genital tract; or exclusion of the possibility of postnatal transmission by a thorough investigation of contact.[6]

Tuberculosis may be suspected in a sick neonate who has clinical features of septicemia, but whose response to adequate doses of appropriate broad spectrum antibiotics and supportive therapy is poor, particularly for those from areas of disease endemicity.[6] An important clue can also be maternal or family history of TB. Indeed in most series as indeed in this index case, mothers are asymptomatic at the time of their infant's diagnosis.[7] Therefore, an inability to identify a contagious source cannot exclude a diagnosis of perinatal TB.[8] In our case, the source of TB transmission that has been identified was the grandmother. Grandmother was diagnosed with pulmonary TB and died 1 year ago. The presence of TB in father was currently unknown. Mother was firstly suspected of having intestinal TB and pulmonary TB, but none of these diagnosis could be established.

Clinically, TB in newborn can mimic and also simulate other infections such as bacterial sepsis.[9] Therefore perinatal TB is particularly difficult to diagnose.[10] Typically, infected infants are born prematurely. Hepatosplenomegaly is found in 76% cases, respiratory distress in 72% cases, fever in 48% cases, and lymphadenopathy in 38% cases.[11-13] Other nonspecific presentations are lethargy, poor feeding, irritability, abdominal distension, and failure to thrive.[3,14]

Symptoms may be present at birth but are usually seen in the second until fourth weeks.[8,11] Other literature stated that the median age at presentation in most reported cases is 24 days (range 1-84 days).[7] In our case, the clinical manifestations of patient were seen when the age of patient 4 weeks and those were included lethargy, breathlessness, fever, and hepatomegaly.

The tuberculin skin test result is unhelpful to establish perinatal TB since it is always negative initially and can take 1–3 months to become positive.[7,10,11] Gastric aspirates in neonates have a higher microbiological yield than in older infants (70%) and are well accepted.[1,7,11,15] Virtually all infants have an abnormal chest radiograph, with nearly half having a milliary pattern.[11,16,17] Ideally, placental and maternal vaginal or endometrial samples from mother should be obtained, but this is frequently difficult and given the later presentations because mothers are mainly found to have TB following diagnosis in the infant.[1,10,18] In our case, supportive examinations reinforced diagnosis towards milliary TB were chest radiograph, AFB on gastric aspirates for 3 days respectively, and culture of gastric aspirate. There was no focal lesion on liver.

Since this is not a common disease, no therapeutic trials have determined the optimal treatment regimen and length.[1] In Indonesia, perinatal TB management was based on *Petunjuk Teknis Manajemen TB Anak Kementerian Kesehatan Republik Indonesia* 2013. Antituberculosis drugs according to this guideline included isoniazid 7-15 mg/kg/day, rifampicin 10-20 mg/kg/day, pirazinamide 30-40 mg/kg/day, and ethambutol 15-25 mg/kg/day. These drug is recommended for 9-12 month.[19,20] Corticosteroids are also used in certain cases, among others, in the case of milliary TB accompanied with shortness of breath.[21] In our case, patient was treated with prednisone and four antituberculosis drugs included isoniazid, rifampicin, pirazinamide, and ethambutol.

Perinatal TB if left untreated or if treatment is commenced late, may have a fatal outcome.[14] Mortality rate is high, around 100% in untreated children and 22% amongst those who receive treatment.[9,10] Other factors that also contributed including prematurity, coinfection with sepsis and HIV. Complete recovery has been described following a standard treatment course of 2 months of 4 drugs (isoniazid, rifampicin, pirazinamide and ethambutol), followed by 4 months of 2 drugs (isoniazid and rifampicin).[1,22] In our case, patient was eventually died. Meningitis, sepsis, and septic shock were also worsened the condition of patient.

SUMMARY

We reported a case of infant aged 28 days, admitted because of breathlessness, fever, and poor feeding. Chest radiograph showed milliary pattern on both lung. Positive result was found for AFB smear on 3 days gastric aspirates respectively and culture of *Mycobacterium tuberculosis* in gastric aspirate. Patient then diagnosed with perinatal TB (milliary TB). Antituberculosis drugs (isoniazid, rifampicin, pirazinamide, and ethambutol) were given simultaneously with corticosteroid and antibiotics. Patient was deteriorated and eventually died after 13 days antituberculosis medication.

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PETUNJUK UNTUK PARA PENULIS

Majalah ilmiah Medicina menerima sumbangan naskah dari para dokter dan ilmuwan di seluruh Indonesia, baik berupa karangan asli, ikhtisar pustaka, laporan kasus, maupun surat-surat untuk redaksi. Naskah yang dikirimkan untuk majalah ilmiah Medicina adalah naskah belum pernah atau tidak akan dikirim ke majalah lain. Bahasa yang digunakan adalah bahasa Indonesia atau Inggris.

Ejaan yang dipakai hendaknya sesuai dengan ejaan pada Kamus Besar Bahasa Indonesia. Jika naskah dalam bahasa Inggris, hendaknya memakai pedoman ejaan *the Oxford English Dictionary* atau *Webster Dictionary*.

Naskah diketik pada kertas kuarto (A_4), berjarak 2(dua) spasi dengan huruf *font*-12 Times New Roman, dengan batas kanan dan kiri 3 cm dan dikirim rangkap 2 beserta *soft copy* dalam bentuk disket baru yang hanya berisi naskah yang relevan saja.

Judul agar dibuat dengan HURUF BESAR dengan huruf *font*-14 Times New Roman, sesingkat mungkin, bersifat informatif dan mampu merangkum isi naskah dan tidak berisi singkatan. Di bawah judul disebutkan nama penulis utama dan penulis pembantu, dicantumkan dengan lengkap tanpa gelar**,** dengan alamat institusi tempat bekerja. Abstrak harus ditulis dalam bahasa Indonesia dan Inggris sebanyak maksimal 250 kata dan disertai dengan 3 sampai 5 kata kunci. Abstrak ditulis dalam format 'satu paragraf'.

Artikel asli berisifat ilmiah dan informatif, disusun sepadat dan sejelas mungkin. Setelah judul, isi karangan asli disusun dalam urutan sebagai berikut: i) Abstrak, ii) Pendahuluan, iii) Bahan dan Metode, iv) Hasil, v) Diskusi dan vi) Simpulan, vii) Pernyataan terima kasih (kalau ada), viii) Daftar Pustaka (berisi 10 tahun terakhir).

Ihktisar pustaka sebaiknya berisikan masalah yang sedang hangat dan isinya akan memberikan pencerahan serta memperluas atau memperdalam wawasan ilmiah pembaca tentang topik bahasan. Setelah judul, ikhtisar pustaka disusun dalam urutan sebagai berikut: i) Abstrak, ii) Pendahuluan (maksimal 1 halaman), iii) Sub-judul menunjukkan gagasan dasar, iv) Ringkasan, v) Daftar Pustaka (berisi 10 tahun terakhir).

Untuk **Laporan kasus,** setelah judul sebaiknya disusun dalam urutan sebagai berikut: i) Abstrak, ii) Pendahuluan (maksimal 1 halaman), iii) Ilustrasi kasus, iv) Diskusi, v) Ringkasan, vi) Daftar Pustaka (berisi 10 tahun terakhir). Ilustrasi yang menyertai naskah berupa gambar, potret, tabel atau grafik. Penggunaan ilustrasi dibatasi pada hal-hal yang relevan dengan isi naskah. Gambar disiapkan pada kertas putih, potret dalam bentuk hitam putih yang mengkilat. Tabel harus dapat berfungsi sendiri tanpa memerlukan tambahan keterangan dari naskah. Tabel memuat bagian-bagiannya, yaitu: a) nomor tabel, b) judul tabel, c) keterangan, dan d) data-data dalam angka. Skala grafik dipilih dengan seksama.

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