

Case Report

Miliary Tuberculosis in Immunocompromised Patient Induced by Imatinib and Steroid

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Abstract

Miliary tuberculosis occurs due to the hematogenous spread of Mycobacterium Tuberculosis from the primary complex. The use of steroid and cytotoxic drugs increases the incidence of miliary tuberculosis. Typical manifestations of miliary tuberculosis is snowstorm appearance seen on chest x-ray and evidence of tuberculosis microorganism from the microbiological examination. It has been reported a 33 years old male patient was admitted to the hospital due to breathlessness, chronic coughing, fever, anorexia, weight loss and night sweating with a "damp shadow sign". Due to chronic myelogenous leukemia and autoimmune hemolytic anemia, the patient is known under imatinib and steroid therapy. There was no specific sign found from the physical examination. Chest x-ray showed snowstorm appearance. The patient underwent GeneXpert MTB/RIF, with the result low MTB detected. The patient was treated with a 2(HRZE)/4(HR) tuberculosis drugs regimen. Imatinib and steroid therapy was discontinued. 2-4 weeks of steroid usage with a daily dose equivalent to prednisone 15 mg increases the risk of activating a latent tuberculosis infection. Imatinib affects the response of T cells to Mycobacterium, thereby triggering tuberculosis reactivation. In this case, the diagnosis has been made from typical manifestations of tuberculosis, snowstorm appearance from the chest x-ray, and low MTB detected from GeneXpert MTB/RIF. It has been recommended to detect latent tuberculosis infection before using steroid and cytotoxic drugs.

Keywords: imatinib, miliary tuberculosis, steroid

Abstrak

Tuberkulosis milier terjadi akibat penyebaran hematogen *Mycobacterium Tuberculosis* dari kompleks primer. Penggunaan steroid dan obat sitotoksik meningkatkan kejadian tuberkulosis milier. Manifestasi klinis khas tuberkulosis milier adalah *snow storm appearance* terlihat dari *chest x-ray* dan bukti adanya mikroorganisme tuberkulosis dari pemeriksaan mikrobiologi. Dilaporkan seorang pasien laki-laki, 33 tahun, datang ke rumah sakit dengan keluhan sesak nafas, batuk kronis, demam, anoreksia, penurunan berat badan dan keringat malam dengan "*damp shadow sign*". Pasien diketahui dalam terapi imatinib dan steroid untuk tatalaksana *chronic myelogenous leukemia* dan *autoimmune hemolytic anemia*. Tidak ditemukan tanda yang khas dari pemeriksaan fisik. *Chest x-ray* menunjukkan *snow storm appearance*. Pasien dilakukan pemeriksaan GeneXpert MTB/RIF, dengan hasil MTB terdeteksi rendah. Pasien diterapi dengan regimen obat antituberkulosis 2(HRZE)/4(HR). Pemberian imatinib dan steroid dihentikan. Penggunaan steroid 2-4 minggu dengan dosis setara dengan prednison 15 mg meningkatkan risiko aktivasi infeksi laten tuberkulosis. Imatinib mempengaruhi respon sel-T terhadap *Mycobacterium*, sehingga memicu reaktivasi tuberkulosis. Pada kasus ini, diagnosis ditegakkan dari manifestasi klinis khas tuberkulosis, *snow storm appearance* dari *chest x-ray*, dan MTB terdeteksi rendah dari pemeriksaan GeneXpert MTB/RIF. Direkomendasikan untuk mewaspadaai adanya infeksi tuberkulosis sebelum pemberian steroid dan obat sitotoksik

Kata kunci: imatinib.miliary tuberculosis steroid

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INTRODUCTION

Miliary tuberculosis (TB) is a type of tuberculosis that occurs due to hematogenous spread of *Mycobacterium Tuberculosis* from the primary complex, where radiologically and histopathologically characterized by an image resembling millet seeds.¹ Miliary TB is a fatal form of disseminated TB. Radiologically, the miliary pattern has been defined as "a collection of tiny discrete pulmonary opacities that are generally uniform in size and widespread in distribution, each of which measures 2 mm or less in diameter".²

Miliary TB accounts for less than 2% of all cases of TB and up to 20% of all extrapulmonary TB cases. Since the 1980s, a changing epidemiological trend has been observed and miliary TB is increasingly being recognized in adults. This epidemiological change is due to the global pandemic of human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS), increasing occurrence of organ transplantation, use of immunosuppressive, steroid, cytotoxic drugs and chronic hemodialysis therapy.^{2,3,4}

The clinical manifestations of miliary TB are non-specific and obscure. The miliary pattern on chest radiograph is the hallmark of miliary TB, seen in the majority of patients. The HRCT may reveal a classical miliary pattern even when the chest radiograph looks apparently normal. Ultrasonography, CT Scan, and MRI examination detect involvement of extrapulmonary TB. The presence of choroidal tubercles are considered to be pathognomonic to miliary TB. Histopathological examination of infected tissues, *mycobacterium tuberculosis* from sputum, body fluids and other tissues showed an overview of tuberculosis.^{5,6}

Hospitalization is required in severe cases of miliary TB. The combination of anti-tuberculosis drugs given is similar to pulmonary TB in general, 2RHZE/4RH, which means that in the first 2 months, 4 drugs will be given (isoniazid, rifampin, pyrazinamide and ethambutol) and 2 drugs (isoniazid and rifampin) in the next 4 months. Corticosteroid administrations are not routinely carried out, only in certain circumstances, mainly due to signs and symptoms of meningitis.^{5,6}

CASE

A 33 years old male patient was admitted to the hospital with breathlessness, chronic coughing, fever, anorexia, weight loss and night sweating with a "damp shadow" sign. Currently, for the past six months, this patient consume imatinib 1x400mg due to chronic myelogenous leukemia and methylprednisolone 12mg/day to treat autoimmune hemolytic anemia. Patient was compos-mentis cooperative, with blood pressure 120/80 mmHg, heart rate 113x/minute, respiration rate 28x/minute, temperature 38,3 °C, BMI 19,19 kg/m². There were no specific signs found from the physical examination. There were no manifestations of extrapulmonary TB. Chest x-ray showed snowstorm appearance. Laboratory examination showed leukocytes and thrombocytes 2.110/mm³ and 17.000/mm³, respectively, blast (-), erythrocyte sedimentation rate 117 mm/hour. The patient underwent GeneXpert MTB/RIF, with the result low MTB detected. Sokal score was 0,5 (low risk). Patient was diagnosed with miliary tuberculosis, chronic phase chronic myelogenous leukemia, and bicytopenia caused by secondary aplasia. Patient was treated with anti-tuberculosis regimen 2(HRZE)/4(HR). Imatinib and steroid were temporarily discontinued.

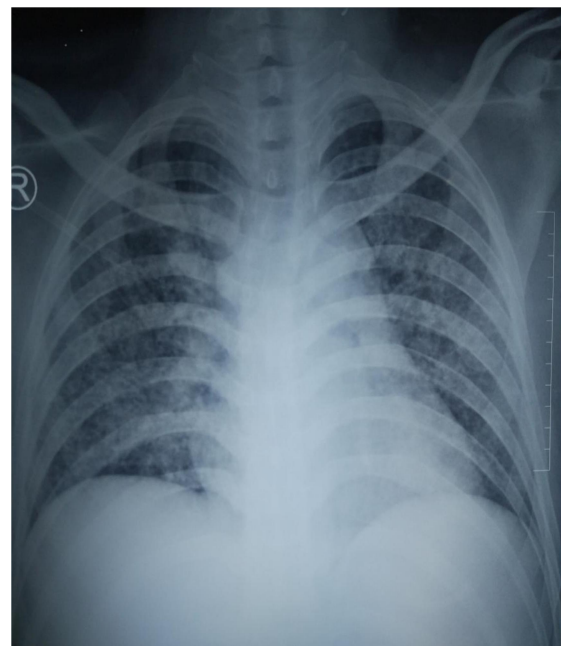


Figure 1. Chest x-ray.

DISCUSSION

A 33 years old male patient with miliary tuberculosis, chronic phase chronic myelogenous leukemia, and bicytopenia caused by secondary aplasia. In this case, diagnosis of miliary TB has been made from typical manifestations of tuberculosis, snowstorm appearance from the chest x-ray, and low detected MTB from GeneXpert MTB/RIF. Patients with miliary TB classically present with fever and increased temperature, especially during the evening for the first several weeks, anorexia, weight loss, weakness, and prominent coughing. Night sweats are common in miliary tuberculosis. A "damp shadow sign" (where sweat engraved the patient's silhouette on the bed, closely resembling a body's shadow) was also described in miliary TB.^{6,7}

The classical miliary pattern on the chest radiograph represents the summation of densities of the tubercles that are perfectly aligned and imperfectly aligned tubercles result in curvilinear densities and a reticulonodular pattern. In about 10% of the cases, the nodules may be greater than 3 mm in diameter ("snowstorm" appearance). Current evidence suggests that the GeneXpert MTB/RIF assay appears to be the promising rapid diagnostic test for patients with miliary TB. GeneXpert MTB/RIF utilizes a heminested real-time PCR assay to amplify the *Mycobacterium tuberculosis* specific sequence of the *rpoB* gene, which is then probed with molecular beacons for mutations within the rifampicin-resistance determining region. It can facilitate rapid diagnosis from clinical specimens in 90 minutes.²

Steroid and cytotoxic drugs were the risk factors of miliary TB in this patient.^{2,3,4} Steroids can inhibit macrophages differentiation, suppressing the production of interleukin-1, interleukin-6, TNF and pro-inflammatory prostaglandins. Steroids suppressed macrophages' bactericidal effects, which also suppressed macrophages' function in controlling bacterial growth.⁸ The 2-4 weeks of steroid usage with a daily dose equivalent to prednisone 15 mg increases the risk of activating latent tuberculosis infection.⁹ Imatinib affects the response of T cells toward *Mycobacterium tuberculosis*, thereby triggering tuberculosis reactivation.^{10,11} It inhibits the activation and proliferation of antigen-induced T cells. Antigen-

specific T-cells and macrophages are vital for protection against *Mycobacterium tuberculosis*.¹²

Latent tuberculosis is defined as a persistent immune response to *Mycobacterium tuberculosis* without any evidence of clinical manifestations of active TB.^{13,14} Data showed that 10% of latent TB becomes active TB, also known as reactivation. The process of reactivation of latent TB to active TB is more at risk in patients receiving cytotoxic drug therapy and long-term use of steroids.^{14,15} TB infection (pulmonary and extrapulmonary) occurs 2-9 times more than the general population in patients with hematological malignancies, including chronic myelogenous leukemia.^{16,17}

There is no gold standard for diagnosing latent TB. The diagnosis of latent TB is carried out using the tuberculin skin test (TST) and interferon-gamma release assays (IGRA).^{18,19} Prevention of active TB through latent TB treatment is one of the components from WHO End TB Strategy.¹⁵

It is recommended to detect the presence or absence of latent TB infection in this patient. If TST or IGRA showed a positive result, latent tuberculosis treatment should be given if there is no sign of active TB found to prevent TB reactivation.²⁰

The patient was treated with anti-tuberculosis regimen 2(HRZE)/4(HR). The combination of anti-tuberculosis drugs given are similar to pulmonary TB in general. There were no approved guidelines for treating concomitant TB infection in CML patients.^{6,17}

CONCLUSION

Incidence of miliary tuberculosis increased in patients under steroid and cytotoxic therapy. It is recommended to detect latent tuberculosis infection before using steroid and cytotoxic drugs. The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are commonly used. The diagnosis of miliary TB was established from the results of the chest X-ray and GeneXpert MTB/RIF.

CONFLICT OF INTEREST

None

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