Pulmonary cryptococcosis in late pregnancy and review of published literature

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Abstract

Naturally occurring maternal immunosuppression increases the risk of infection by a variety of pathogens during pregnancy and the postpartum period. Pulmonary cryptococcosis during pregnancy is relatively rare. Here we report on two cases of pulmonary cryptococcosis during pregnancy and puerperium. Both cases were successfully treated using oral fluconazole after parturition to avoid fetal toxicity. For the two patients, the placentas were checked and found to be pathologically normal, and the cryptococcal serum antigen in both infants was negative. Pulmonary cryptococcosis should be considered during differential diagnosis as a possible cause of abnormal chest shadow in pregnant patients.

Key words: *Cryptococcus neoformans*, fluconazole, pregnancy, pulmonary cryptococcosis, immunosupresion

Introduction

Abnormal chest shadows are an important part of differential diagnosis of infectious diseases such as community-acquired bacterial, viral pneumonia, pulmonary tuberculosis or mycoses and non-infectious diseases such as malignancy, cryptogenic organizing pneumonia and pulmonary embolism [1, 2]. Diagnosis of chronic or mild infections caused by tuberculosis or cryptococcosis in otherwise healthy, immunocompetent patients is sometimes delayed due to its insignificant symptoms.

C. neoformans is recognized as the third most common fungal pathogen in autopsied cases in Japan [3]. In particular, cryptococcal infection occurs not only in immunocompromised patients such as those with AIDS, organ transplants, hematological malignancies and corticosteroid treatment, but occasionally in healthy individuals [4 - 8].

Due to naturally occurring maternal immunosuppression, women are known to be at higher risk of infection by a variety of pathogens during the perinatal period. Here we report on two cases of pulmonary cryptococcosis during the perinatal period, both of which were successfully treated with oral fluconazole after parturition to avoid fetal toxicity.

Case report

Case 1

A 30-year-old female was admitted to our hospital in her 38th week of pregnancy with complaints of hemosputum but in otherwise good health. Chest X-ray revealed nodular lesions with cavities in the right middle lung fields (Fig. 1A), and chest CT scan revealed multiple nodular lesions under the right pleura with cavitary lesions in the lower lobes (Fig. 1B, Fig. 1C). On physical examination, body temperature was 36.5°C, heart rate was 75 beats/min and blood pressure was 110/75 mm Hg. Respiratory sounds were normal vesicular. The patient had no peripheral lymphadenopathy, skin lesions or neurological deficits. The peripheral white blood cell count was 7200/mm^3 with a differential count of 58% neutrophils, 32% lymphocytes, 1% basophils, 6% monocytes and 3% eosinophils. The serum CRP level was elevated at 3.53 mg/dl. Other laboratory examination results were as follows: total protein, 5.3 g/dl; serum albumin, 3.4 g/dl; serum creatinine, 0.4 mg/dl; blood urea nitrogen, 7.0 mg/dl; serum lactate dehydrogenase, 147 IU/l. Serum glucose concentration and liver function tests were normal. Analysis of arterial blood gas on room air was as follows: pH, 7.445; PaO_2, 112.2 Torr; $PaCO_2$, 31.9 Torr and HCO_3^-, 31.9 mmol/L. We suspected pulmonary tuberculosis or cryptococcosis due to the chest radiograph manifestations. In

bacteriological examination, Gram and acid fast staining, cultural test of sputum revealed no microorganisms and negative, respectively, The serum cryptococcal antigen level, however, was positive at a titer of 1:8. The patient was diagnosed clinically with pulmonary cryptococcosis. Lumbar puncture was performed to rule out cryptococcal meningoencephalitis, and analysis of recall revealed no evidence of central nerve system infection. Treatment began after parturition with oral fluconazole (FLCZ) at 400 mg/day for 3 months. Breastfeeding was avoided during antifungal treatment. The clinical outcome for this patient was good, and no adverse effects were apparent. The pregnancy was uneventful and the fetus suffered no damage. After 3 months treatment was discontinued, the serum cryptococcal antigen level became negative. The patient showed no recurrence at follow-up examination more than one year after the discontinuation of antifungal therapy.

Case 2

A 29-year-old female was in good health until the third trimester of her pregnancy when she came to the clinic with complaints of cough with sputum. Symptoms were mild and stable, so she was observed without examination and therapy. The pregnancy was uneventful and the fetus suffered no damage. Four months after parturition, an abnormal chest shadow was identified in chest X-ray and further examination was

recommended. The chest X-ray showed multiple nodular lesions in both lung fields (Fig. 2A), and a CT scan of the chest revealed multiple nodular shadows mimicking pulmonary tuberculosis in both upper and lower lobes, with no pleural effusion and enlargement of lymph nodes (Fig. 2B, Fig. 2C). On physical examination, body temperature was 36.5°C, heart rate was 72 beats/min and blood pressure was 100/56 mm Hg. Respiratory sounds were normal. The patient had no peripheral lymphadenopathy, skin lesions or neurological deficits. Laboratory results showed that peripheral white blood cell count was 5900/mm^3 with a differential count of 55% neutrophils, 35% lymphocytes, 1% basophils, 8% monocytes, 1% eosinophils. The serum CRP level was elevated at 0.10 mg/dl. Other laboratory results included: total protein, 5.8 g/dl; serum albumin, 3.4 g/dl; serum creatinine, 0.8 mg/dl; blood urea nitrogen, 13.0 mg/dl; serum lactate dehydrogenase, 301 IU/l; serum glucose concentration, normal; liver function tests, normal. Arterial blood gases on room air were: PaO_2, 99.2 Torr; $PaCO_2$, 42.8 Torr; pH, 7.418; HCO_3^-, 27.1 mmol/L. A clinically documented diagnosis of pulmonary cryptococcus was made since the serum cryptococcal antigen level was positive at a titer of 1:256. Bronchoscopy was performed, and BAL fluid was positive for cryptococcal antigen at a titer of 1:64 although the culture was negative. Results from lumbar puncture suggested the presence of

cryptococcal meningoencephalitis due to a positive titer of 1:8 in a cryptococcal antigen test. Oral FLCZ at 400 mg/day and flucytocine (5-FC) at 1500 mg/day were begun and continued for 3 months. Breastfeeding was avoided during antifungal treatment. The patient showed no recurrence at follow-up examination more than one year after discontinuation of antifungal therapy. After 6 months treatment was discontinued, the serum cryptococcal antigen level became negative.

Discussion

In the first case reported here, the patient was in the 38th week of pregnancy, and in the second case, the patient was postpartum when she was diagnosed. In the first case, bronchoscopy was not performed due to pregnant status of the patient. *Cryptococcus neoformans* was not isolated by cultural test although the specimen from the infection site was acquired in the second case. There is a possibility that the pulmonary lesions and the amount of organism were small to be detected.

These two patients were considered to have pregnancy-related immunosuppression since alterations to the immune system persist throughout pregnancy, peak during the third trimester and return to baseline three to five months postpartum. Although *C. neoformans* was not isolated from these patients, clinically documented diagnoses were

made based on antigen tests and images.

Immunosuppression during pregnancy is well-documented [2]. The pregnant host undergoes several physiological immune system adjustments designed primarily to prevent rejection of the antigenically different fetus. In fact, during pregnancy, it is possible to demonstrate depression of first-set skin graft rejection and a reduction in delayed-type hypersensitivity skin test responses. The most important factor for acquiring cryptococcal and other infections is the alteration of maternal T-cell activity [9, 10]. Natural killer cell-mediated cytotoxicity is also diminished during pregnancy [11]. Decreases in the absolute number of CD4 cells and the CD4/CD8 ratio during pregnancy have been reported [12]. Moreover, IgG levels decline [13], and polymorphonuclear leukocytes exhibit decreased chemotactic responses during pregnancy [14].

Therapeutic decision-making for pregnant patients raises very important issues regarding risks and benefits of the available antifungal agents versus potential complications of the disease. Most of the cases of cryptococcosis during pregnancy were treated by amphotericin B (AMPH-B) and showed good outcome for mother and infant (Table 1). In pregnancy, all of the azole antifungal drugs are categorized as class C according to the U.S. Food and Drug Administration (FDA) and should be used with

caution because of the risk of fetal malformation. Azoles are contraindicated for pregnant women and should only be used during pregnancy when the benefits outweigh the risks. Oral FLCZ appears to be a safe and effective alternative therapy after delivery for less severely ill patients who can be managed on an outpatient basis. However, azoles are excreted in breast milk, and the risks of those compounds to neonates are not well studied [30]. Therefore, for pregnant women with limited pulmonary cryptococcosis and no evidence of disseminated disease, close follow-up without antifungal therapy until postpartum is recommended [26]. In the first case, since there was no evidence of disseminated disease and pulmonary cryptococcal lesions were limited, we observed her condition carefully every one to two weeks and only began antifungal treatment with oral FLCZ after parturition. In the second case, spinal fluid was positive for cryptococcal antigen, and disseminated cryptococcosis was confirmed. Although combination therapy with AMPH-B and 5-FC is recommended for disseminated cryptococcosis [31], we treated with oral FLCZ and 5-FC since they exhibit good penetration to spinal fluid and because synergistic effects have been reported [32, 33].[13,14] Breastfeeding was avoided in both cases to prevent toxicity in the infants due to azoles. We measured the FLCZ concentration in the breast milk of the first patient and confirmed that the FLCZ concentration was high. Moreover, we

considered whether intrauterine transmission of *Cryptococcus* could have occurred, since there have been reports of mother-to-child transmission of cryptococcosis, with formation of lesions in the placenta [34, 35].[15,16] For the two patients in the present study, the placentas were checked and found to be pathologically normal, and the cryptococcal serum antigen in both infants was negative.

In conclusion, pulmonary cryptococcosis due to maternal immunosuppression should be considered during differential diagnosis as a possible cause of abnormal chest shadow in pregnant patients. For successful maternal and fetal outcomes, cryptococcosis should be observed carefully during pregnancy and antifungal treatment delayed until after parturition.

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Figure legends

Fig. 1A: Chest X-ray film of Patient 1 on admission revealed nodular lesions in right middle and lower lung fields.

Fig. 1B, 1C: Chest CT films of Patient 1 on admission revealed nodular lesions under the right pleura. High resolution chest CT films showed the nodular lesion with cavity in the right middle lobe.

Fig. 2A: Chest X-ray film of Patient 2 showed multiple small nodular lesions in both lung fields.

Fig. 2B, 2C: Chest CT films of Patient 2 revealed multiple nodular lesions in both upper and lower lobes without pleural effusion or enlargement of mediastinal lymph nodes.

Table 1. Twenty three cases of cryptococcosis during pregnancy

Age	Onset	symptoms	Diagnosis	Type of Infection	Treatment	outcome		others	Year/reference
						Mother	Infant		
19	2nd	ataxia	India ink stain, culture (CSF)	Meningitis	AMPH-B 25-50mg/day	Well	Well	Recurrence was seen	1959/15
26	2nd	Headache, diplogia	India ink stain, culture (CSF)	Meningitis	AMPH-B	Well	Well	Recurrence was seen	1962/16
33	1st	Headache, drowsiness	Culture (CSF, blood)	Meningitis	AMPH-B 1500mg(total)	Death	Death	Complicating septicemia	1972/17
16	1st	Head and neck pain	India ink stain, Culture (CSF)	Meningitis, pulmonary disease	AMPH-B 415mg(total), sequential 5-FC 340g	Well	Well	Placenta was small, contained many infarcted area	1972/17
28	Post partum	Headache	India ink stain, culture (CSF)	Meningitis	AMPH-B 1960mg(total)	Well	Well	Complicating sarcoidosis	1972/18
unknown	2nd	unknown	unknown	unknown	AMPH-B	Well	Well	none	1973/19
24	3rd	Nausea, vomiting, blurred vision	India ink stain, Culture (CSF)	Meningitis	AMPH-B 2507mg(total)	Well	Well	none	1981/20
13	1st	Headache, nausea	India ink stain, Culture (CSF)	Meningitis	AMPH-B 2242mg(total)	Well	Well	none	1981/20
30	2nd	Headache, visual disturbance	India ink stain Culture, Cr antigen (CSF)	Meningitis	AMPH-B 0.3mg/kg/day+ 5-FC 4g/day	Well	Well	none	1983/21
30	3rd	Headache	Culture (blood)	Disseminated disease	unknown	Death on 2nd partum day	Well	Mother had AIDS	1989/22
19	2nd	Headache, nausea	India ink stain, Cr antigen (CSF)	Meningitis	AMPH-B 15mg/day + 5-FC6g/day	Well	Well	VP shunt placement	1991/23
18	3rd	Headache, nausea	India ink stain, Culture (CSF)	Meningitis	AMPH-B 50mg/day +5-FC3g/day	Well	Well	none	1996/24

Age	Onset	symptom	Diagnosis	site of Infection	Treatment	outcome		others	Year/reference
						Mother	Infant		
28	3 week postpartum	Headache, dry cough	TBLB, serum Cr antigen	Pulmonary disease	FLCZ 20mg/day	Well	Well	Serum Cr antigen decreased 1:512→1:8	1998/25
32	3rd	Chest pain, fever	TBB, serum Cr antigen	Pulmonary disease	AMPH-B 500mg (total) + 5-FC	Well	Well	Left upper lobe nodule	1998/26
28	2nd	Chest pain	Needle aspiration	Pulmonary disease	None	Well	Well	none	1998/26
30	3rd	Chest pain	TBB, serum Cr antigen	pulmonary disease	AMPH-B 1000mg(total), FLCZ 6mo, ITCZ 2mo	Well	Well	Right lower lobe numerous nodule	1998/26
35	1st	cough	Open lung biopsy, serum Cr antigen	pulmonary disease	AMPH-B 2093mg(total)	Well	Well	Lingula and right lower lobe nodule	1998/26
19	3rd	meningitis	Culture(CSF), serum Cr antigen	Meningitis	AMPH-B	Well	Well	none	1998/26
29	2nd	sleepiness	autopsy	Meningitis	Dexamethasone, mannitol	Death	Well	Caesarian delivery	1999/27
35	2nd	dyspnea	Histological examination	Massive lymphadeno pathy	Intravenous FLCZ 400mg/day	Well	Well	CT-guided biopsy was performed	2006/28
26	2nd	Fever, cough	India ink stain(CSF), Culture (CSF, blood)	Meningitis	FLCZ(66days)	Death	Death (by cryptoco ccosis)	Mother had AIDS	2008/29
30	3rd	Hemosput um	Serum Cr antigen	Pulmonary disease	FLCZ 400mg/day	Well	Well	Brest feeding was stopped during therapy	2008/current report
28	Post partum	Chest abnormal shadow	Serum Cr antigen	Pulmonary disease	FLCZ400mg/day +5-FC 1500mg	Well	Well	Brest feeding was stopped during therapy	2008/current report

Table 1. (continue)

Abbreviation; CSF; cerebrospinal fluid, Cr; cryptococcal, AMPH-B; amphotericin-B FLCZ; fluconazole, 5-FC; flucytosine, AIDS; acquired immunodeficiency syndrome TBB; transbronchial biopsy TBLB; transbronchial lung biopsy

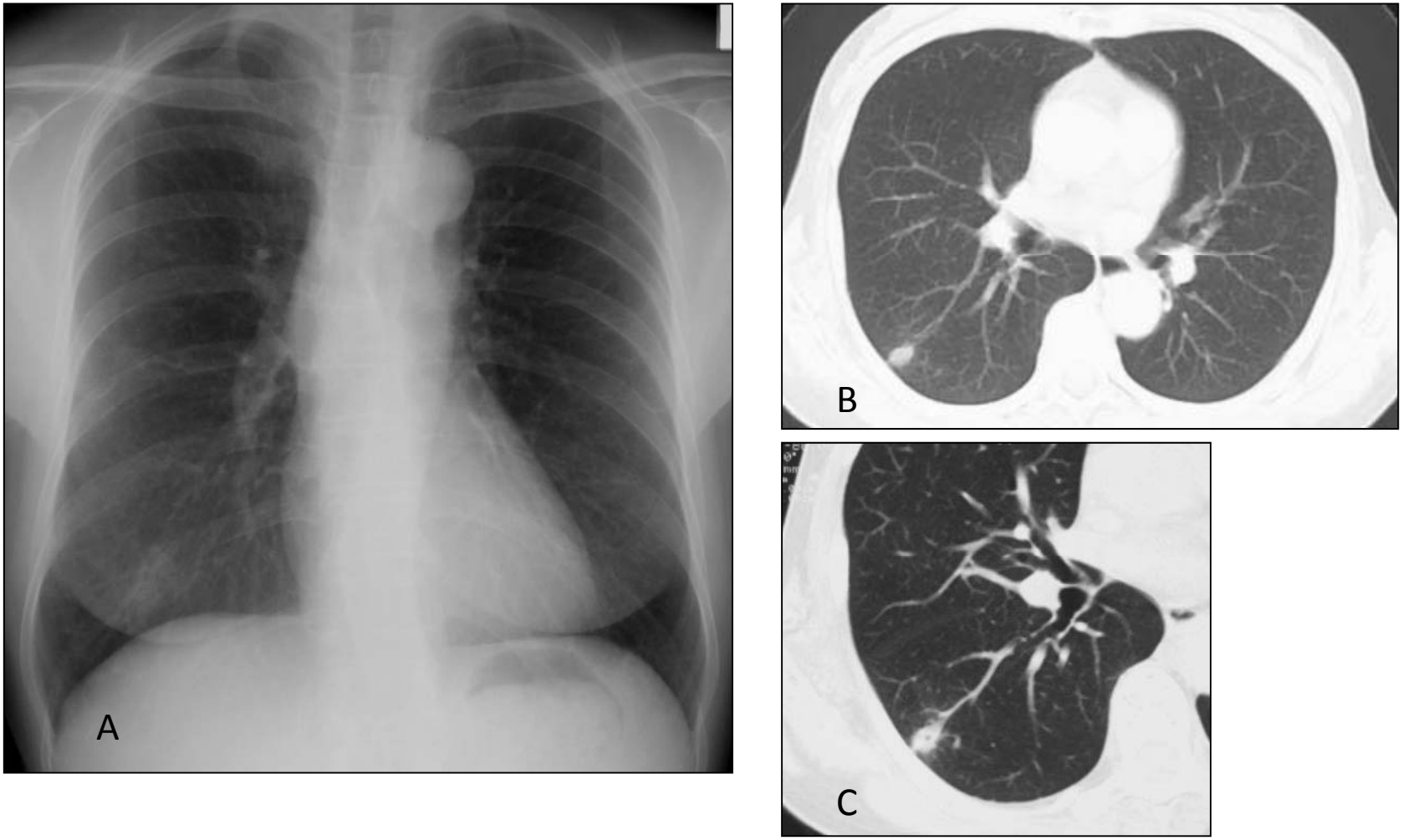

Figure. 1

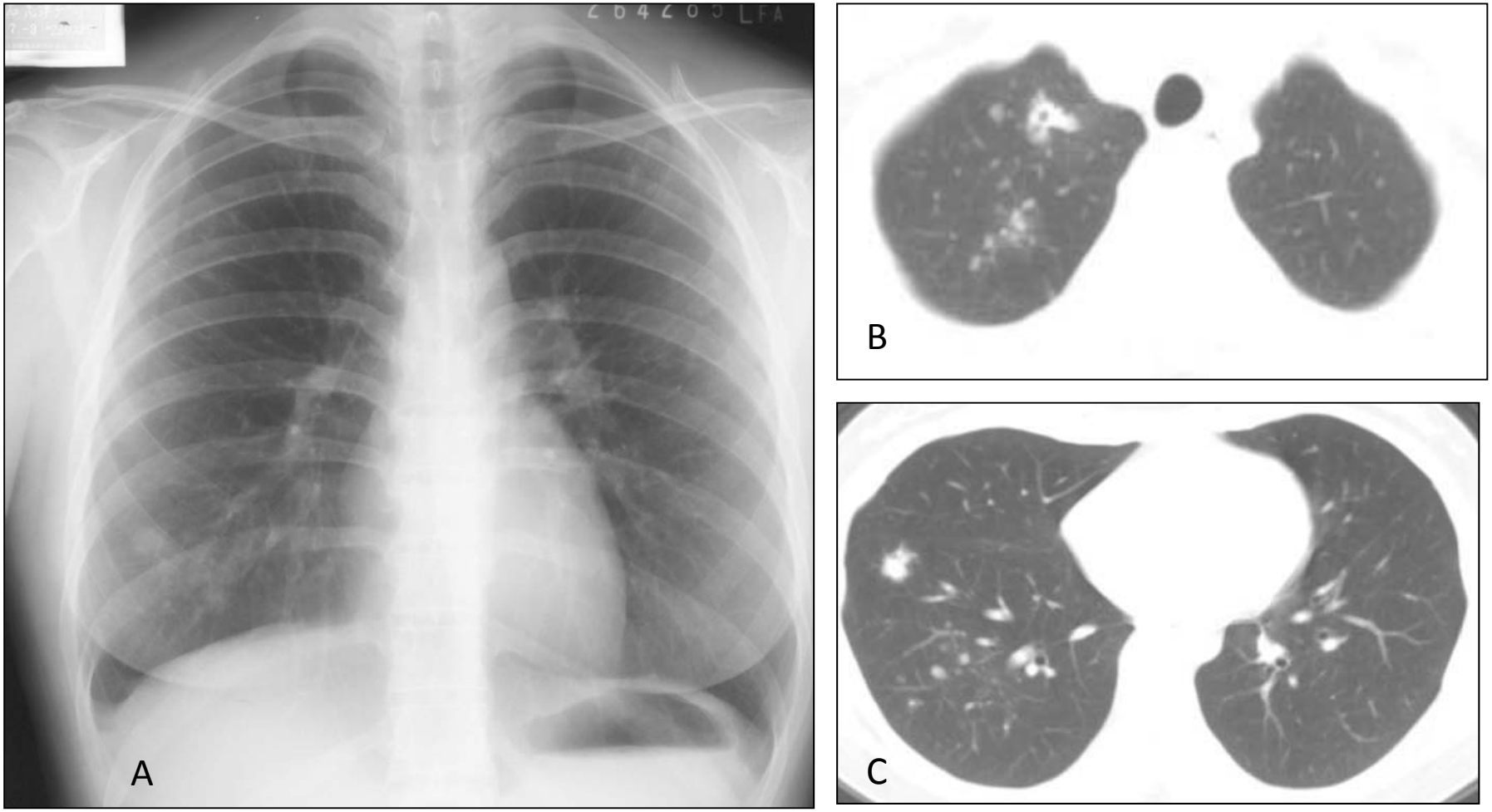

Figure. 2