

A rare infection of the respiratory system with erythema nodosum in a young nun

**Antonis Antoniadis,
Pavlina Stogiou,
Dimitris Bobotas,
Aikaterini Mitka,
Stavros Trifon,
Chrysoula Karagiannidou**

General Hospital of Serres, Pneumology
Clinic

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- *Coccidioides immitis*

SUMMARY. This is a case report of a young woman, a nun, who presented with fever, arthralgia, intense non-specific symptoms and erythema nodosum. Despite the non-typical radiological features, the careful review of her medical and personal history was decisive for the diagnosis and treatment. The patient suffered from Coccidioidomycosis, which is a rare infection in Greece. The appropriate treatment led to immediate clinical and laboratory improvement. The three-year follow-up did not show no any residual lesions or disorders. *Pneumon 2008; 21(4):407–411*

INTRODUCTION

Coccidioidomycosis is a fungal infection caused by the two species of the genus *Coccidioides*: *Coccidioides immitis* (CA group) and *Coccidioides posadasii* (non-CA group)^{1,2}. Coccidioidomycosis is endemic in the south-western United States and locations in Mexico and Central and South America, where the winters are relatively mild and the soil is alkaline^{3,4}. The disease in non-endemic regions is typically related to travel⁷ or to exposure to fomites from the endemic areas⁸.

Travellers to the endemic areas contract the pulmonary disease when they inhale arthroconidia-endospores of *C. immitis*.

Coccidioidomycosis can appear in various forms: acute primary pulmonary disease, chronic pulmonary disease, rheumatoid disease and disseminated disease.

CASE REPORT

A 21 year-old woman, who had been a nun for the past five years, presented for examination at the hospital with fever of 15 days duration, up to 38° C, mostly in the afternoon, a nonproductive cough, night sweats and fatigue. Weight loss and arthralgia were ascertained. Three days before the onset of fever she experienced an acute thoracic pain on her left hemi thorax that worsened with respiratory movements. Seven days later an exanthem developed on her shins, diagnosed as erythema nodosum. She

Correspondence:

Antonis Antoniadis,
Pneumology Clinic, General Hospital of Serres
Tel: 23210 94607, Fax: 23210 94624

had a negative medical history and she did not smoke.

Clinical examination revealed tachypnoea (28 respirations/minute) without pathological pulmonary sounds, tachycardia (120 beats/minute), clear S_1 , S_2 sounds and no palpable lymph nodes. Her abdomen was smooth with no masses and with normal intestinal sounds. The liver and the spleen were not palpable. There were bilateral lesions of erythema nodosum on her shins (Figure 1).

Chest X ray depicted a mild enlargement of the left hilus and infiltrates adjacent to the left hilus (Figure 2).

The patient was admitted for further examinations in the pulmonology clinic. The first laboratory tests showed: WBC 13,500/mm³ (neut 75.2%, lym 14.9%, mono 8.3%), Ht 36.1%, Hb 11.9%, Plt 421,000/μL, ESR 70 mm/h, glucose



FIGURE 1. Erythema nodosum.



FIGURE 2. Chest Xray at the time of admission.

88 mg/dL, urea 19 mg/dL, Creatinine 0.5 mg/dL, CPK 48 IU/L, LDH 162 IU/L, SGOT 15 IU/L, SGPT 8 IU/L, K 4.3 mEq/L, Na 143mEq/L. Urinary analysis was normal.

Arterial blood gas analysis showed mild hypoxaemia (pO_2 : 72 mmHg), pCO_2 : 36 mmHg and pH: 7.44.

The computerised tomography (CT) of the chest revealed pulmonary infiltrates at the top of the left lower lobe with aerobronchogram, satellite punctate nodules with both discrete and poorly defined borders, locally confluent, and enlargement of the left hilar lymph nodes (Figure 3).

Based on the afternoon fever, the sweats, the fatigue and the erythema nodosum in combination with patient's age and radiographic evidence tuberculosis was considered to be the most likely diagnosis, and for that reason she was started on treatment with Rifabacin, Isoniazid, Pyrazinamide and Ethambutol, but the differential diagnosis included the following diseases that are accompanied by erythema nodosum:

- Idiopathic erythema nodosum
- Streptococcal infection
- Mycoplasma infection
- Pharmaceutical erythema nodosum
- Tuberculosis
- Sarcoidosis
- Inflammatory bowel disease
- Coccidioidomycosis

Based on the differential diagnosis the laboratory tests included: ASTO, IgM against Mycoplasma, Ra test, ACE, ANCA, T3, T4, TSH, HbsAg.

Ocular examination showed no pathological findings. Heart and abdomen ultrasonography were normal. All the laboratory tests were normal. The Mantoux test was negative.

Despite the anti-tuberculosis treatment, the patient's condition worsened, with deterioration of the fatigue and malaise, to such degree that she was not able to get up from her bed, while the fever and arthralgia persisted.

A careful review of her personal history revealed that the patient had recently travelled in the United States, where she had stayed for thirty days in Arizona, returning a month before admission.

Based on her travel to this area, endemic for *Coccidioides sp.*, the negative Mantoux test, the deterioration of her clinical condition despite anti-tuberculosis treatment and the clinical and radiological findings that were consistent with Coccidioidomycosis, the anti-tuberculosis treatment was discontinued and fluconazole was administered in a dosage of 200 mg, twice a day.

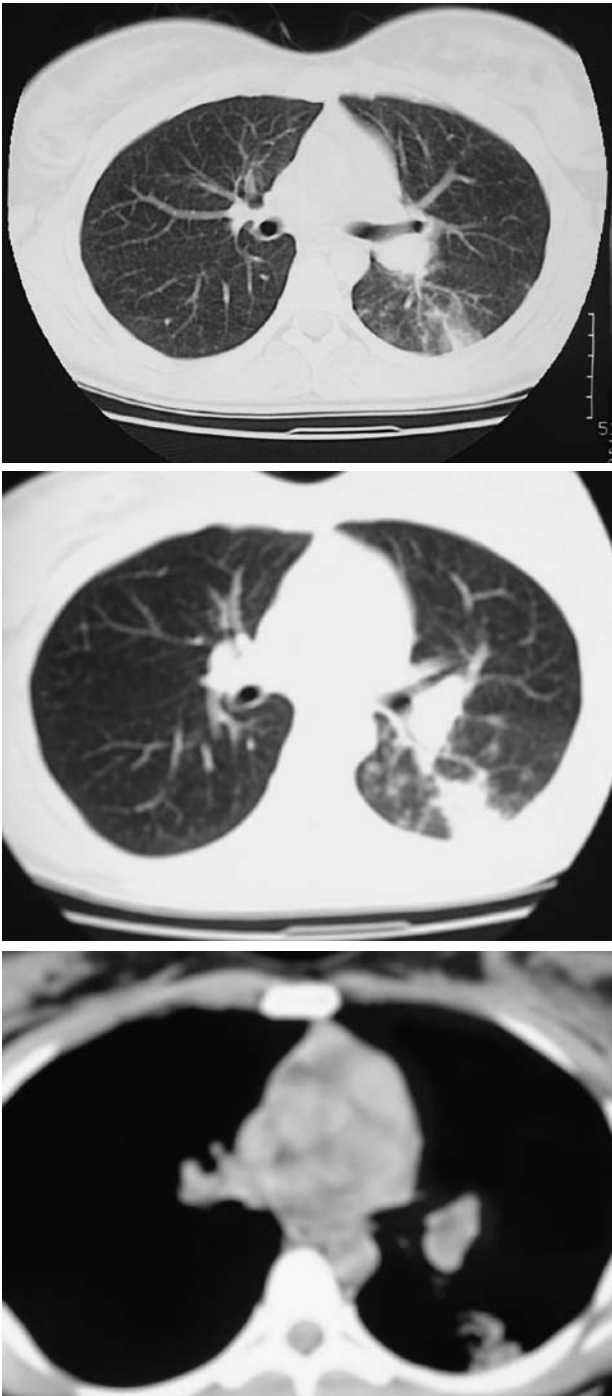


FIGURE 3. Computer tomography at the time of admission.

Before the start of treatment, serological examinations for mycotic infections were sent to a Greek laboratory and to a laboratory of the University of California specializing in *Coccidioides sp.* The response to the treatment was impressive. On the second day the fever dropped

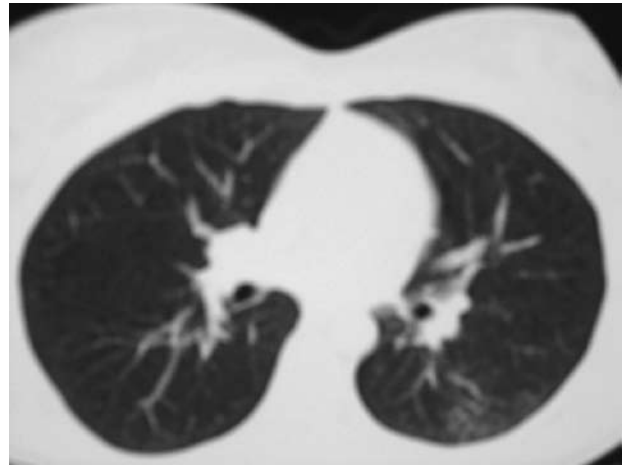


FIGURE 4. Computerised tomography after therapy.

and gradually the malaise and fatigue abated. The arthralgias and erythema nodosum disappeared within two weeks.

Both the laboratories confirmed the diagnosis of coccidioidomycosis. The qualitative immunodiffusion method detected IgM and IgG antibodies against *Coccidioides sp.* The quantitative CF study for IgG showed a titer of 1:4 in the first sample, 1:8 in the second and 1:2 in the third. It became negative six months later. PCR examination was positive for *Coccidioides sp.*

Fluconazole was continued in a dose of 200 mg twice daily for a month, 100 mg twice daily for another month and 100 mg once a day for one last month.

The duration and the cessation of the treatment were based on the reduction of the antibody titers against *Coccidioides sp.*

Three years later, the patient is in perfect clinical condition, with no residual lesions or disorders.

DISCUSSION

Coccidioidomycosis is a fungal infection that was first identified in Argentina in 1892¹. It is caused by the two species of the genus *Coccidioides*: *C. immitis* (ex CA group) and *C. posadasii* (ex non-CA group)^{1,2}. Coccidioidomycosis has a high infectious activity and the routes of entry of *Coccidioides sp.* are the respiratory system and the skin. The disease is endemic in the southwestern United States and locations in Mexico and Central and South America, where the winters are relatively mild and the soil is alkaline^{3,4}. The annual incidence is estimated to be 150,000 in the United States⁵. The disease in non-endemic regions

is typically related to travel⁶ or to exposure to fomites from the endemic areas⁷. In such cases diagnosis is often delayed because the infection is not considered initially⁸. This also happened in the reported case, which was initially treated as pulmonary tuberculosis.

Coccidioidomycosis is caused by the inhalation of arthroconidia, or on rare occasions after percutaneous implantation of arthroconidia into underlying tissue. Commonly, two peak periods of activity occur in Arizona (spring and end of summer) and one occurs in California (end of summer)⁹. The patient reported here stayed in a monastery in Arizona for a month, from the middle of September until the middle of October. Fewer exposures occur during the wetter and less dusty months^{10,11}.

Coccidioidomycosis can appear as acute primary pulmonary disease, chronic pulmonary disease, rheumatoid disease or disseminated disease.

The inhalation of arthroconidia causes acute pulmonary coccidioidomycosis. About 60% of clinical infections occur with few or no respiratory symptoms and the remaining 40% of patients that are symptomatic may present symptoms ranging from "flu-like" to those of progressive pneumonia⁹. Symptoms usually begin within 7 to 21 days of inhalation of arthroconidia. Patients complain of fever, nonproductive cough, chest discomfort, malaise and fatigue. The patient presented here presented with similar symptoms one month after her journey to Arizona.

Exanthemata develop in 10- 50% of patients, mostly erythema nodosum, but also toxic erythema or erythema multiforme¹³. Erythema nodosum is the classic presentation in endemic areas and is prognostically suggestive of a low risk of dissemination, since it correlates with development of cell-mediated immunity¹⁴⁻¹⁶.

Pulmonary disease appears in 25% of cases, with pleuritic pain, cough, usually nonproductive, fever, arthralgia and myalgia similar to the symptoms of community-acquired pneumonia. Chronic pulmonary infection can occur, particularly in hosts who are immunocompromised or those with underlying diabetes mellitus^{12,14}.

The radiological findings are non specific in the acute primary pulmonary disease, including segmental or lobar infiltrates, hilar lymphadenopathy and small pleural effusions. About 5% of patients may have nodules, cavitation, bronchiectasis or calcifications. The reported case had some of these radiological findings. Imaging studies depict cavities and fibrosis in chronic pulmonary infection, similar to those of tuberculosis and histoplasmosis.

Disseminated coccidioidomycosis is estimated to occur in less than 5% of symptomatic patients and in less than

1% of all infections. It may occur months to several years after the primary infection⁹. This occurs in patients who are immunosuppressed from treatment with high-dose corticosteroid, anti-TNF and chemotherapy or, even more often in patients with T-cell dysfunction¹²⁻¹⁴.

Coccidioidomycosis may affect the joints (rheumatologic type) causing synovitis. The knees are the most common joints involved, followed by the ankles and the wrists^{13,14}.

Elevated ESR and eosinophilia may be seen in Coccidioidomycosis. IgM antibody becomes measurable within one (50% of cases) to three (90% of cases) weeks of onset. IgG antibodies become measurable sometime between the second and the third weeks of onset or up to several months later. The titer is usually related to the degree of infection⁹. Titers above 1:32 suggest severe extrapulmonary disease or disseminated disease. In the reported case the IgG titer was 1:4 on the first sample, 1:8 on the second and 1:2 on the third, and it became negative after 6 months, which is consistent with a mild clinical evolution of the disease.

Asymptomatic patients do not need therapy in most cases⁹. Indicators of severe illness for which to consider therapy of acute primary coccidioidomycosis include the following: continuous fever for longer than one month, night sweats for longer than three weeks, weight loss of greater than 10%, persistent hilar lymphadenopathy, large or bilateral pulmonary infiltrates, IgG titer >1:16¹⁷⁻¹⁹. However, some experts propose treatment for all symptomatic patients¹⁷⁻¹⁹. In the reported case, persisting fever and significant fatigue and malaise indicated the need for treatment.

Typical antifungal therapy for acute primary pulmonary infection consists mainly of oral azoles, in a dose of 200-400 mg per day for three to six months^{9,17-19}. In the reported case the patient received fluconazole for three months. The duration and the cessation of the treatment were based on the reduction of the antibody titers against *Coccidioides sp* and the improvement of patient's clinical condition.

Amphotericin B is used only in serious coccidioidal infection⁹ and during pregnancy because the azoles may be teratogenic. Mortality is extremely uncommon in primary coccidioidomycosis.

In conclusion, coccidioidomycosis is quite often diagnosed lately in non-endemic areas, due to the current trends of more frequent travelling. Diagnosis is typically delayed in these cases because the infection is not considered initially. For these reasons, travellers visiting the

endemic areas should be aware of the risk of acquiring coccidioidomycosis, and doctors should be familiar with the presenting signs and symptoms of the disease.

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