

Hodgkin disease is derived from an alteration in the maturation and activation of B cells in the lymph nodes. It is characterized by the presence of lymphadenopathies. Approximately 25% of patients have general symptoms consisting of the so-called B symptoms: fever, night sweats, and weight loss. Diagnosis is obtained by biopsy, showing characteristic Reed–Sternberg cells on cytology. The nodular sclerosis variant is the most common and has the best prognosis. Treatment is based on chemotherapy and radiation therapy, depending on staging.

The combination of sarcoidosis and lymphoma is unusual, and may be derived from a disordered immune system. Lymphoma-sarcoidosis syndrome was described by Brincker in 1986 after conducting 2 studies, the first in the Danish Clinical Epidemiology Institute, and another subsequent study. Brincker observed that the frequency of lymphoma in patients with pulmonary sarcoidosis was significantly higher than in the general population, the most common being Hodgkin disease, followed by non-Hodgkin lymphoma and other hematological cancers. He also concluded that sarcoidosis normally precedes the lymphoproliferative process by a short period of around 24 months; the inverse order is rarely seen.⁴

The development of sarcoidosis after receiving treatment for a lymphoproliferative process may be due to a hyperresponse of the immune system against the tumor cells.⁵ Patients with sarcoidosis may also experience an exacerbation after receiving anticancer treatment. Sarcoid reactions have been reported that are histologically identical to sarcoidosis, and these might be a marker of antitumor response mediated by macrophages activated by T cells.⁶ In conclusion, sarcoidosis and lymphoproliferative processes are diseases in which differential diagnosis can be complicated, but it

is important to remember that both diseases may be found in the same patient, either consecutively or simultaneously.

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Atypical *Chlamydia psittaci* Pneumonia. Four Related Cases[☆]



Neumonía atípica por *Chlamydia psittaci*. Cuatro casos relacionados

To the Editor,

Psittacosis is a globally distributed zoonotic disease caused by *Chlamydia psittaci* (*C. psittaci*), an intracellular bacteria.¹ Birds constitute its main reservoir and the mechanism of transmission is direct contact or inhalation of respiratory secretions or dry feces of infected birds.² Individuals with occupational or recreational exposure to various birds have a greater risk of infection.³ Psittacosis generally occurs sporadically, but outbreaks have been reported.² Presentation varies from subclinical infection to severe sepsis and multisystemic involvement.^{3,4} We describe an outbreak of 4 cases of *C. psittaci* pneumonia, the focus of infection being a store selling birds (Table 1).

Case 1

A 47-year-old man was admitted with a 5-day history of dyspnea and fever. On admission, he presented tachypnea and crackles in the right lung base, respiratory failure (RF) (PaO₂ 55 mmHg), neutrophilia (91%), elevated C-reactive protein (CRP) (49 mg/dl), procalcitonin (PCT) 1 mg/ml, and alveolar infiltrate in the right

lower lobe. Antibiotic treatment with ceftriaxone, levofloxacin and doxycycline was administered for 2 weeks, followed by oseltamivir for 5 days. After 24 h he developed respiratory failure and progressive radiological infiltration, renal failure and shock, so was admitted to the intensive care unit (ICU). Invasive mechanical ventilation was initiated, with noradrenaline 0.4 mcg/kg/min and extrarenal depuration. In view of the lack of response, venovenous extracorporeal membrane oxygenation support (ECMO) was required. Progress was slow and weaning prolonged, and the patient was discharged from the ICU after 60 days, and from the hospital 81 days after admission. *C. psittaci* DNA was detected in respiratory samples (nasopharyngeal exudate and tracheal aspirate) by polymerase chain reaction (PCR). No other microorganisms were found, including influenza virus. Immunofluorescence testing for *C. psittaci* serology was positive (IgG seroconversion 1:256 after 14 days from the first sample).

Case 2

A 22-year-old man was admitted with a 1-week history of fever, dry cough, and general malaise. Physical examination showed fever, arterial hypertension, tachycardia, and crackles in the entire right hemithorax. The patient presented respiratory failure (PaO₂ 53 mmHg), neutrophilia (87%), elevated CRP 58 mg/dl, clotting disorders with prothrombin activity 55%, and multilobar infiltrate in right lung. He received high-flow oxygen therapy in the ICU. Ceftriaxone, levofloxacin and doxycycline were administered for 2 weeks. *C. psittaci* serology was positive, with IgG seroconversion (1:256) in convalescent serum. All other microbiological results

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Table 1
Comparative Characteristics of the Cases.

	Case 1	Case 2	Case 3	Case 4
Exposure	Customer	Employee	Employee	Employee
Place admitted	ICU	ICU	Hospital ward	Hospital ward
Days admitted	60+21	6+3	5	5
CRP (mg/ml) admission	49	58	41	39
CRP (mg/ml) 72 h	46	21	6	9
Chest radiograph admission	Infiltrate both lower lobes	Alveolar infiltrate 3 right lobes	Alveolar infiltrate right lower lobe	Alveolar infiltrate right upper and middle lobe
Chest radiograph at 1 month	Bilateral infiltrate consistent with ARDS	Normal	Normal	Normal
Complications	Septic shock Multiorgan failure	Septic shock	Severe sepsis	Severe sepsis
<i>C. psittaci</i> serology	+	+	+	+

CRP: C-reactive protein; ICU: Intensive Care Unit.

were negative, including *C. psittaci* PCR of nasopharyngeal exudate. Clinical symptoms and radiological signs resolved after 6 weeks.

Case 3

A 20-year-old man was admitted with a 1-week history of fever, cough with white sputum, and general malaise. Physical examination revealed fever and crackles in the right lung base. Clinical laboratory results showed neutrophilia (84%), CRP 41 mg/dl and prothrombin activity 58%. Chest radiograph revealed alveolar infiltrate in the left lower lobe. Treatment began with azithromycin (discontinued on day 3), ceftriaxone, and doxycycline lasting 10 days. The patient showed clinical, analytical and radiological improvement. IgG seroconversion (1:256) observed in convalescent serum. All other microbiological results were negative, including *C. psittaci* PCR of nasopharyngeal exudate. At 1 month, the patient was asymptomatic and radiological images were resolved.

Case 4

A 52-year-old woman was admitted with a 1-week history of fever, cough, and mucous expectoration, with a tendency toward arterial hypertension. Respiratory failure (PaO₂ 57 mmHg), neutrophilia (87%), raised CRP (39 mg/dl), procalcitonin 30 ng/ml, and right bilobar infiltrate. Treatment began with ceftriaxone and azithromycin and continued for 10 days. PCR of nasal exudate was negative for *C. psittaci*, and IgG seroconversion (1:256) was observed in the convalescent serum. All other microbiological results were negative. At 1 month, the patient was asymptomatic and radiological images had resolved.

Outbreaks of psittacosis have been described primarily in individuals exposed to birds, for example, veterinary surgeons and employees of stores selling animals.⁴ Other outbreaks of psittacosis associated with occupational exposure in bird farms have been described.^{5,6} We report an outbreak of 4 cases of psittacosis with different degrees of severity, ranging from mild pneumonia to multiorgan failure requiring ECMO and a prolonged ICU stay. All of the subjects visited a bird store which sold *Agapornis* (love birds) that showed signs of disease. The infection may be indistinguishable from other atypical pneumonias, so the history of exposure to birds was key to guiding the suspected diagnosis.^{3,7} Severity may vary widely, from mild respiratory infection to full-blown disease, requiring intensive care and even ECMO.³ Diagnosis is based on the clinical examination, epidemiological history, and laboratory confirmation using direct (culture, PCR) or indirect (serology) methods.¹ Given the complexity of culturing *C. psittaci* (biosafety level 3) and the unavailability of commercial molecular methods (PCR), diagnosis is based on serologies.^{1,8} In

the cases discussed here, serological confirmation was obtained when specific IgG seroconversion was detected at 14–17 days after the initial sample, except for case 3, in whom it was detected in a third sample obtained at 37 days. In all cases detection of specific IgM in the acute phase was negative. DNA detection of *C. psittaci* was performed in respiratory samples from all patients using a non-commercial PCR technique,⁹ but this was positive in the most severe case only. *C. psittaci* infections are very rare in humans and molecular tests are not standardized, so these techniques have not been widely evaluated in clinical samples, and sensitivity and specificity data are scant.¹⁰

Tetracyclines, macrolides and quinolones are the best empirical treatments for intracellular bacteria.¹¹ Our cases were initially treated in different hospital departments (emergency room, UCI) by different physicians, thus explaining the different treatment regimens. Antibiotic cover was maintained on the pulmonology ward with a betalactam and an antibiotic with intracellular action. Improvement is generally observed 48 h after starting antibiotic treatment.²

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Tuberculosis Among Portuguese Living Abroad[☆]



Tuberculosis en los portugueses residentes en el extranjero

To the Editor:

Tuberculosis (TB) is a major health problem worldwide, and effective control remains a challenge. Risk is especially high for migrants due to the difficulties they may encounter in the host country: disrupted social networks, social exclusion, reduced accessibility to health care, lack of egalitarian participation in society, lack of trust, understanding or respect for the system.¹ Portugal, with more than two million citizens living abroad, is the European Union country with the highest number of emigrants per capita.²

In order to characterize Portuguese emigrants diagnosed with TB when returning to their homeland, we performed a retrospective analysis of all such individuals diagnosed with TB in 2014 in Northern Portugal, evaluating both clinical and social-demographic data. New TB cases were identified from the national tuberculosis surveillance system and local TB centers were contacted for more detailed information. Continuous variables were described by median and interquartile range (25th–75th percentile) and categorical variables by relative frequencies (in percentage).

During the studied period, 17 returned Portuguese emigrants were diagnosed with TB in Northern Portugal. Socio-demographic, life-style and clinical characteristics are presented in Table 1. The median age at diagnosis was 43.0 years, and 88.2% of the patients were male. The majority of patients were immigrants in low-burden TB countries ($n=13$, 76.5%).³ Median residence in the host country was 42.0 months (4.3–138.0). The majority of patients worked in the construction industry ($n=9$, 52.9%). One patient was a health care worker. Fifty-three percent ($n=9$) of patients shared a house with non-family members, most of them sharing a room with another co-worker ($n=6$, 66.7%).

Recent exposure to pulmonary TB (previous 2 years) was reported by 3 patients (17.6%), 1 of whom reported exposure in Portugal to a close family member and 2 to a cohabitant member in Angola and France respectively. None of the 3 patients had undergone contact tracing or screening for TB. One patient reported a history of pulmonary TB. None of the patients were taking immunosuppressive drugs. Median time from symptom onset to diagnosis was 85.5 days (59.5–147.0) and from return to Portugal to diagno-

sis was 14.0 days (10.0–37.0). Six patients (35.3%) sought medical advice in their host country due to symptoms, but TB diagnosis was not suspected or pursued. Among patients who did not seek medical advice in their host country ($n=11$, 64.7%), 72.7% ($n=8$) were working in the construction industry and reported having been strongly advised to return to Portugal for medical advice by their employers. It was unclear whether this was due to their being in an illegal situation or if there were any other barriers to health care. All 16 patients with pulmonary TB had positive smear sputum at the time of diagnosis. The majority of patients reported multiple symptoms of tuberculosis: cough was the most frequently reported symptom ($n=14$, 82.4%) followed by night sweats ($n=9$, 52.9%) and weight loss ($n=9$, 52.9%).

This study characterizes returned Portuguese emigrants diagnosed with TB in their country of origin. Despite the limited number of patients, our findings give further insight into the challenge of effectively managing TB in migrant populations. Study subjects had resided in their host country for more than 2 years, on average, suggesting that exposure to TB probably occurred in that country. Three patients reported recent exposure to pulmonary TB, 2 of them in the host country and 1 in Portugal, and none of them were properly investigated. This situation raises some questions about the challenges surrounding contact tracing of TB patients abroad, and suggests that communication procedures between countries could be improved.

The median time between symptom onset and diagnosis observed in this study was 85.5 days, in line with some published data. In 1 study in a TB outpatient clinic in Northern Portugal in 2014, median time from onset of symptoms to diagnosis was 36 days,⁴ although national data from the same year report a median time of 104 days.⁵ In 2014, a total of 817 cases of TB were reported in the tuberculosis national surveillance system in northern Portugal, with a median time from onset of symptoms to diagnosis of 96 days in all cases. Data from France reported a median delay between symptoms and diagnosis of 97 days,⁶ and a systematic review found an average delay in TB diagnosis of 61 and 68 days in high-income and low-middle income countries, respectively.⁷

Another interesting finding in this report is the short interval (14 days) between return to Portugal and TB diagnosis. This suggests that once in Portugal, many patients sought medical advice as soon as possible, and were diagnosed in a short period of time. In fact, 64.7% of patients did not seek medical advice in their host country, despite the presence of symptoms.

Improved understanding of the barriers that migrants face in TB diagnosis is important from a perspective of worldwide management of the disease. This insight can also help each country optimize TB diagnosis in the migrant population and strengthen communication channels between countries.

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