

Case report

A rare pulmonary pathology complicated with an unusual condition

A 73-year-old male presented to the emergency department complaining about fatigue, night sweats, lack of appetite and weight loss for the past 2 months. His baseline weight was 47 kg and his height was 1.78 m (body mass index of 14.83 kg·m⁻²), while at presentation he weighed 39 kg. From his history, he underwent gastrectomy 31 years ago for stomach cancer. He was a smoker (55 pack-years), with no history of alcohol consumption or any other known pathological condition. Despite his gastrectomy, he did not suffer from symptoms suggesting reflux disease. 2 years ago, his daughter suffered from pulmonary tuberculosis, but he was not checked at that time with either a Mantoux test or chest radiograph. Physical examination revealed crackles in both lungs. His heart rate and blood pressure were normal. Because of his gastrectomy, he was on treatment with B12 and folic acid supplements and on presentation he did not reveal megaloblastic anaemia. From his laboratory examinations, his white blood cells were normal (9780 cells·μL⁻¹ (68.4% neutrophils, 21.7% lymphocytes)) while his C-reactive protein was elevated (8.87 mg·dL⁻¹).

Despite his obviously impaired nutritional status his serum albumin was slightly above the lower normal level (3.67 g·dL⁻¹). His chest computed tomography (CT) revealed infiltrations bilaterally, signs of incipient pulmonary fibrosis with thickened interlobular septa, centrilobular nodules and loss of volume of the left lower lobe (figure 1). His blood gas analysis revealed hypoxaemia; therefore, he was admitted to hospital and initiated intravenous antibiotic treatment with ampicillin/sulbactam plus azithromycin.

Cite as: Kotoulas SC, Manika K, Piliandis G, *et al.* A rare pulmonary pathology complicated with an unusual condition. *Breathe* 2019; 15: 121–127.

Task 1

Based on the patient's history, clinical findings and laboratory and imaging tests, which is the most probable diagnosis?

- a) Pulmonary infection with *Mycobacterium tuberculosis*
- b) Cryptogenic organising pneumonia
- c) Pulmonary infection with *Haemophilus influenzae*
- d) Bronchoalveolar carcinoma



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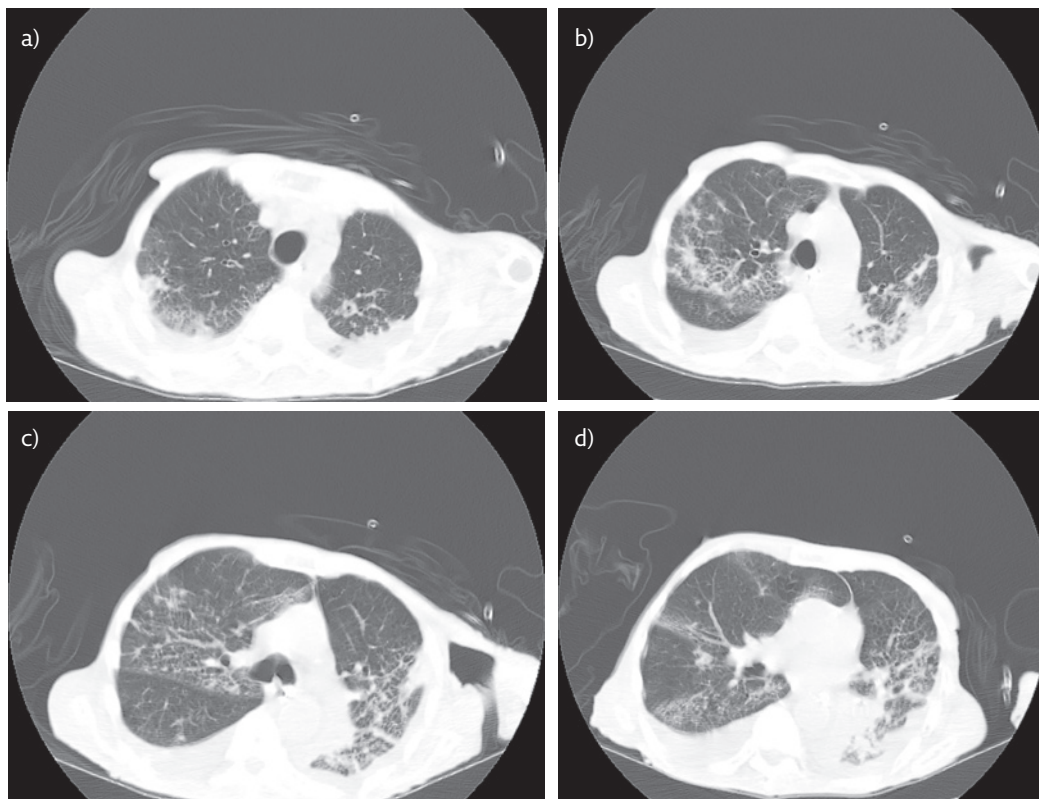


Figure 1 Chest CT revealing infiltrations bilaterally (a–d), signs of incipient pulmonary fibrosis with thickened interlobular septa (b–d), centrilobular nodules (c, d) and loss of volume of the left lower lobe (c, d).

Answer 1

a) Based on the patient’s history of gastrectomy, his daughter’s history of pulmonary tuberculosis and his clinical presentation (fatigue, night sweats, lack of appetite and weight loss), together with his chest CT findings, the most probable diagnosis was initially attributed to pulmonary tuberculosis.

A Mantoux test was performed and two sputum and one bronchoalveolar lavage (BAL) samples were sent for analysis during the first 3 days of his hospitalisation. However, Ziehl–Neelsen staining and Xpert MTB/RIF assay, along with his Mantoux test, were all negative. The BAL sample was also negative for other bacteria and fungi, and cytology was negative for malignancy. BAL fluid differential cell count revealed an elevated percentage of lymphocytes (21%) and neutrophils (14%). Serological testing for connective tissue disease (CTD) was undertaken, but this was also negative.

Since community-acquired pneumonia (CAP) could not be excluded, as a single or concomitant infection, a suitable regimen of antibiotic treatment for CAP was initiated without using a fluoroquinolone, due to the high suspicion of tuberculosis. Blood cultures were also sent to investigate for a possible pathogen.

On the fourth day, the patient presented with confusion, disorientation and hypoglycaemia (glucose: 51 mg·dL⁻¹). Since he had never presented neurological symptoms in the past, his symptoms were originally attributed to his hypoglycaemia as a result of his prolonged undernutrition; thus, intravenous dextrose water solution 5% and parenteral nutrition were initiated. His cerebrospinal fluid was negative for infection and magnetic resonance imaging (MRI) of his brain revealed contrast enhancement of the thalamus and mammillary bodies (figure 2). Right after his brain

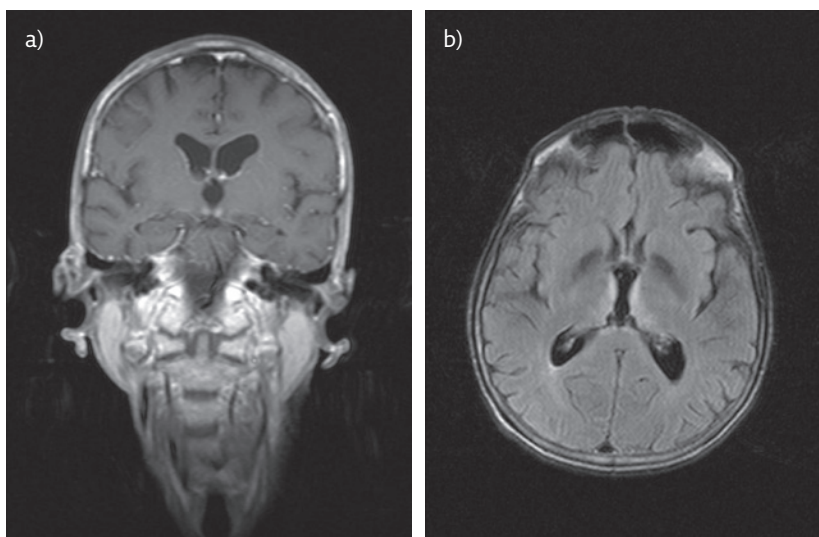


Figure 2 Brain MRI revealing a) contrast enhanced mammillary bodies, and b) contrast enhancement of the thalamus.

MRI, the patient developed severe haemodynamic instability (heart rate: 143 beats·min⁻¹; blood pressure: 78/47 mmHg) unresponsive to vasopressor therapy. His electrocardiogram did not reveal any other pathological findings apart from sinus tachycardia, his serum troponin level remained normal and his heart ultrasound revealed a left ventricle ejection fraction of 65% and an elevated estimated pulmonary artery systolic pressure of 48 mmHg. His lactic acid was elevated at 7.3 mmol·L⁻¹ (normal level: <2.5 mmol·L⁻¹) and his oxygenation also deteriorated. His chest radiograph showed an image of pulmonary oedema (figure 3) and his arterial blood gases were arterial oxygen tension=58.2 mmHg, arterial carbon dioxide tension=46.2 mmHg, pH=7.235, bicarbonate=18.9 mmol L⁻¹, arterial oxygen saturation=89.8% while breathing with a non-rebreather; therefore, he was intubated and transferred to the intensive care unit (ICU) where his antibiotic therapy changed to meropenem.



Figure 3 Chest radiograph revealing bilateral infiltrates attributed to pulmonary oedema.

Task 2

Which is the most possible cause of the patient's deterioration?

- a) Diabetic ketoacidosis
- b) Pulmonary emboli
- c) Acute wet beriberi
- d) Septic shock

Answer 2

c) The patient's rapid deterioration after the initiation of intravenous dextrose water solution and parenteral nutrition, and the development of lactic acidosis and hypotension resistant to vasopressor therapy, together with the findings from his brain MRI, which were compatible with Wernicke's encephalopathy, set the suspicion of acute wet beriberi. This was confirmed by his significantly low serum thiamine levels of $24 \text{ nmol}\cdot\text{L}^{-1}$ (normal range: $74\text{--}222 \text{ nmol}\cdot\text{L}^{-1}$).

Beriberi is a condition caused by thiamine deficiency. Wet beriberi is the term used for its effects on the cardiovascular system. Thiamine deficiency results in a decrease in the activity of the Krebs cycle enzymes, for which is a cofactor, leading to anaerobic glycolysis and tissue accumulation of pyruvate and lactate, which decrease peripheral resistance and cause resistant hypotension [1]. Intravenous glucose and parenteral nutrition intensify these metabolic procedures and could lead to acute wet beriberi [2, 3], as in this case. The accumulation of pyruvate and lactate also increases the blood flow in veins, which consequently increases cardiac preload, which together with myocardial dysfunction results in congestive heart failure and pulmonary oedema [1]. Moderate pulmonary hypertension is also common in wet beriberi, as in our case, in which an additional risk factor for pulmonary hypertension was the possible chronic underlying pulmonary parenchymal pathology, as exhibited by the findings of the patient's chest CT. Left ventricle ejection fraction and cardiac output is preserved or usually increased in wet beriberi, as the main pathophysiological mechanism leading to congestive heart failure is the decrease in systemic vascular resistance and the increase of venous blood flow [1]. Acute or Shoshin beriberi is a rapidly evolving and fulminant form of wet beriberi, characterised by tachycardia, resistant hypotension and lactic acidosis [2], as in our case. Wet beriberi responds well on treatment with thiamine and its haemodynamic abnormalities are usually reversed rapidly after the initiation of treatment [2].

Dry beriberi is the term describing the effects of thiamine deficiency on the nervous system, a form of which is Wernicke's encephalopathy. The clinical symptoms of Wernicke's encephalopathy are the triad of mental confusion, oculomotor dysfunctions and ataxia. Mental confusion can vary from apathy and irritability to stupor and coma. Oculomotor dysfunctions include nystagmus and ophthalmoparesis. Ataxia affects predominantly the trunk and lower limbs and appears as difficulty in standing and walking. These symptoms are usually not found together in the same patient and in up to 19% are all absent [3], as in our case. Other neurological symptoms of thiamine deficiency include tingling or loss of feeling in the feet and hands, neuropathic pain, vomiting, difficulty in speaking and paralysis.

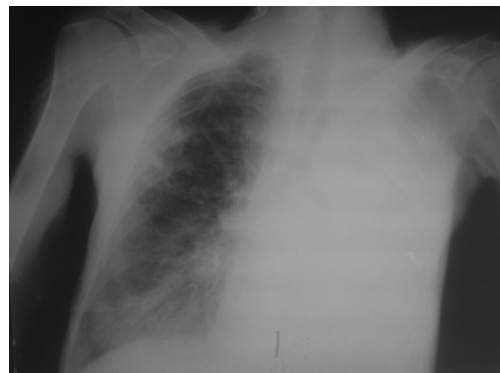


Figure 4 Chest radiograph revealing a complete atelectasis of the left lung.

Septic shock could not be excluded from the differential diagnosis. The patient presented new infiltrates in his chest radiograph and resistant hypotension. Although the new infiltrates were attributed to pulmonary oedema, it is often difficult to distinguish between cardiogenic pulmonary oedema, pneumonia and acute respiratory distress syndrome by chest radiography because of its low specificity. In addition, the lack of signs of pneumonia, such as fever, purulent sputum or leukocytosis, could not rule out the diagnosis, as in the elderly or immunocompromised these signs may be absent. Blood cultures, which were sent and came back negative, could also not be conclusive because of their low sensitivity. Since the patient deteriorated after 4 days of hospitalisation and presented the signs described above, it seemed wise to cover for nosocomial pneumonia. Meropenem was selected because in our setting there is high incidence of hospital-acquired pneumonia caused by Gram-negative bacteria sensitive only to carbapenems and polymyxins.

Intravenous thiamine treatment was initiated immediately after diagnosis, but the patient did not stabilise until the fifth day of his admission to the ICU, when he was extubated and remained haemodynamically stable without supportive treatment.

2 days later, the patient's condition deteriorated again. He re-established a type II respiratory failure, combined with metabolic acidosis (mixed acidosis), haemodynamic instability and oliguria. His chest radiograph revealed a complete atelectasis of his left lung (figure 4); therefore, he was re-intubated.

Task 3

Which is the most possible cause of the patient's new deterioration?

- a) Relapse of his acute beriberi
- b) Septic shock due to nosocomial pneumonia caused by Gram-negative bacteria resistant to meropenem
- c) Pulmonary infraction
- d) Pharmaceutical reaction to meropenem

Answer 3

b) The patient's thiamine level was elevated to normal levels after his treatment with intravenous thiamine ($87 \text{ nmol}\cdot\text{L}^{-1}$), while pulmonary infraction is related with peripheral, rather than central atelectasis. His new findings were not typical of a drug-related adverse reaction, but are common in septic shock due to Gram-negative bacteria. The complete atelectasis of his left lung could have been caused by the development of new purulent secretions. Indeed, his bronchial secretions culture developed *Klebsiella pneumoniae* resistant to meropenem and the patient passed away due septic shock, within 36 h.

Surprisingly, a few days after his death, MGIT cultures from his original two sputum samples and his BAL sample came back positive (Bactec MGIT 960 system; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and *Mycobacterium fortuitum* was isolated.

Task 4

Which risk factors did the patient have for developing pulmonary infection by a non-tuberculous mycobacterium (NTM)?

- a) Immunocompromise due to his chronic malnutrition
- b) Gastrectomy (possible asymptomatic reflux disease)
- c) Smoking (possible underlying pulmonary disease)
- d) All of the above

Answer 4

d) Although NTM were thought to cause human infections mainly in immunocompromised patients, they are now recognised as significant pathogens in immunocompetent hosts as well [4]. In a recent study, several risk factors for NTM infections were identified, such as: history of tuberculosis, active, or within the previous year; tobacco use; alcohol abuse; history of intravenous drug use; homelessness; imprisonment; immunosuppression; and chronic lung diseases including chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis, and others [5]. More specifically for *M. fortuitum*, gastro-oesophageal disorders such as gastrectomy or reflux disease have been reported as risk factors for pulmonary infection [6]. Despite the fact that *M. fortuitum* is occasionally cultured from sputum samples, it rarely causes pulmonary disease [7]. However, in this case, the patient presented many risk factors. Gastrectomy is a predisposing factor for reflux disease and both of them for pulmonary infection by *M. fortuitum* [6]. Even though the patient did not suffer from suggestive symptoms, it is well established that reflux disease could remain asymptomatic in many patients and could lead to development of idiopathic pulmonary fibrosis (IPF). As mentioned earlier, the patient was a heavy smoker, which is by itself a risk factor for pulmonary infection by NTM [5]. Moreover, smoking predisposes for chronic pulmonary disease. Pulmonary function tests could have revealed an obstructive (as in COPD) or a restrictive (as in IPF) pattern, but were not performed because the patient was too weak to cooperate. The patient's chest CT revealed signs of an underlying pulmonary disease, which is also a risk factor for pulmonary infection by NTM [5], but those findings, along with the findings of his BAL differential cell count were not specific of a certain disease pattern. Furthermore, serological testing for CTD was negative and more invasive diagnostic techniques, like lung biopsy, were not performed, because of the patient's rapid deterioration. Last but not least, the patient was badly malnourished even before his infection, a fact which is well known to cause immunodeficiency [8, 9]. Among others, malnutrition affects T-cell-mediated immune responses by diminishing the expression levels of interleukin (IL)-12, IL-18 and IL-21, molecules that induce the differentiation of T-cells related to the immunological cellular response (T-helper cell (Th1) response) and the production of cytokines related to the immunological cellular response (Th1 cytokines), such as IL-2 and interferon- γ , which also have been found to be decreased in plasma because of malnutrition. The decreased expression of Th1 cytokines probably deteriorates the immunological Type 1 (cellular) response leading to inability to eradicate infections [9].

Discussion

Beriberi is a condition that results from severe and chronic thiamine deficiency, which is usually caused by severe malnutrition, with two main types in adults: wet beriberi, which affects the cardiovascular system [10]; and dry beriberi, which affects the nervous system [11]. Both types are usually met in third world countries, because of shortage of appropriate feeding [12]. Nowadays, in the developed world it is relatively rare [13]. The most common causes are alcoholism (32.26%), digestive system disease and surgery (29.03%), imprisonment (9.68%), furosemide administration (6.45%), a mixture of factors (16.13%), other (3.23%) and unknown (3.23%) [14].

To the best of our knowledge, this is the first case of acute beriberi in a patient with infection by an NTM and perhaps as a result of it. The patient was already malnourished before his infection, because of his gastrectomy. His brain MRI showed signs of Wernicke's encephalopathy, a form of beriberi, indicating that he had a chronic thiamine deficiency, even though he had never presented any neurological symptoms. Apart from his gastrectomy, pulmonary infection by *M. fortuitum* could have been contributing to the patient's malnutrition causing his lack of appetite and weight loss during the 2-month period before his admission. This deterioration may have led to the emergence of his acute beriberi. Therefore, in the case presented here, gastrectomy and NTM infection created a vicious cycle leading to an acute-over-chronic presentation of thiamine deficiency.

M. fortuitum, which belongs to the rapidly growing mycobacteria (RGM), is a well-known cause of skin, soft tissue, post-surgical wound and catheter-related infections [7, 15]. Pulmonary infection by this species is relatively rare; however, its incidence increases in patients with gastro-oesophageal disorders such as gastrectomy or reflux disease [6], which is also a risk factor for beriberi [16].

NTM are a varied group of environmental organisms that may cause human disease [5]. Between 1993 and 1996 *M. fortuitum* was the second most isolated potentially pathogenic species of NTM in the USA after *Mycobacterium avium* complex, with a frequency of 4.6–6 isolates per 1000000 population [15]. In Greece between 1990 and 2013, out of 73 patients meeting the American Thoracic Society 2007 criteria for pulmonary disease by NTM [15], eight (10.96%) suffered from RGM but only two (2.74%) from *M. fortuitum* [17], a fact that demonstrates the rareness of pulmonary disease by this species. For confirmation of pulmonary infection due to NTM, the responsible pathogen should be isolated in more than one respiratory tract samples, as in this case in which *M. fortuitum* was cultivated in three different samples, because NTM can often be found in such samples in the context of colonisation [7, 18]. Furthermore, NTM infection should be kept in mind in patients with possible pulmonary tuberculosis, as in our case,

especially when risk factors are present, since their clinical and radiological findings are identical [19, 20].

This case highlights the consequences of severe malnutrition. Malnutrition can lead to severe neurological deficiency, life-threatening cardiovascular complications and immunological impairment, resulting in rare respiratory infections or lethal nosocomial pneumonias, as in the case presented. Unfortunately, hospital-acquired pneumonia is a major nosocomial complication, particularly in settings with high prevalence of highly resistant pathogens, like ours. Apart from that, it seemed that our patient probably suffered from an underlying chronic pulmonary disease, which we were unable to identify, but could have

predisposed him to an infection by *M. fortuitum*. Maybe there was a connection between that and his gastrectomy and/or thiamine deficiency, perhaps by an asymptomatic reflux disease. Finally, it seems plausible to claim that beriberi and *M. fortuitum* pulmonary infection occurred in the same patient, both as late complications of his gastrectomy and subsequent malnourishment. Gastrectomy in this patient succeeded in confronting a life-threatening condition, *i.e.* his stomach cancer, but its long-term consequences proved unpredictable and severe. In this setting the consequences of malnutrition should not be underestimated and complications of gastrectomy should be kept in mind during the patients' lifetime.

Affiliations

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Conflict of interest

None declared.

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