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And then there were none

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PRESENTATION OF THE CASE AND DIFFERENTIAL DIAGNOSIS

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A 75-year-old woman presented to hospital referring recurrent episodes of dyspnea accompanied by wheezing and a productive cough for the past six months. She also mentioned a weight loss of 3 kg. She reported no chills, headache, joint pains, muscle aches, heartburn, nausea or vomiting. On examination, the patient appeared to be well. Axillary temperature was 37.5ºC and the respiratory rate 20 breaths per minute. She had scattered low-pitched wheezes in both lungs and fine crackles in the right posterior base. The remainder of the examination was unremarkable.

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Symptoms of chronic cough and wheezing initially bring to mind a diagnosis of asthma. However, to present with asthma at this age would be uncommon, and the presence of persistent low-grade fevers begs the consideration for an ongoing inflammatory or infectious process. The clinical presentation, along with her age and gender fit the epidemiology of eosinophilic granulomatosis with polyangiitis (formally known as Churg-Strauss syndrome).

When evaluating chronic infections, it´s important to determine whether the patient is immunocompromised or has underlying comorbidities such as COPD and bronchiectasis that change the lung structure and allow pathogens to gain a foothold. Certain predisposing conditions favor particular pathogens that characteristically affect specific populations (e.g. *Nocardia* spp. in patients on high doses of steroids). Chronic infections that present with respiratory symptoms include mycobacterial (Tuberculosis and non-tuberculous mycobacteria –NTM), fungal and parasitic infections in the immunocompetent, with the addition of viral (e.g. adenovirus) causes in the immunosuppressed hosts.

A common infection-trigger of recurrent wheezing is allergic bronchopulmonary aspergillosis (ABPA). *Aspergillus* skin test and antibodies, plus elevated IgE levels would aid in the diagnosis. Given the long course of presentation, pneumonia due to *Cryptococcus spp.* is a possibility, which triggers reactive wheezing and external airway compression. If the patient has travelled abroad, there could be concerns for endemic mycoses, which rarely cause wheezing. Parasitic infections can cause Loffler syndrome (a respiratory illness with blood eosinophilia and diffuse pulmonary infiltrates commonly associated with parasitic infections). The patient would have had to travel to the Americas, Caribbean or other endemic areas.

Drug induced pneumonitis or chronic eosinophilic pneumonia should also be considered. A partial tracheal obstruction or disseminated lymphangitic carcinomatosis could also explain bilateral wheezing. Space occupying and constricting processes in the mediastinum, such as bulky lymphadenopathy, mediastinal granuloma, lymphoma, fibrosing mediastinitis or even a teratoma, can cause wheezing through external compression. However, the patient's age makes this possibility significantly less likely. A thorough history focusing on exposures and risk factors is essential.

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The patient's medical history included severe persistent asthma diagnosed fourteen years earlier, for which she received salmeterol xinafoate/fluticasone propionate, tiotropium bromide and theophylline and was closely fol-

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lowed by a pulmonologist. Her medications also included esomeprazole, calcium/vitamin D3 (1 g/880 IU daily) and denosumab (every six months) for osteoporosis. The patient lived in an urban area, had no animals nor travelled abroad in the previous years. She had been admitted to another hospital in the previous month and diagnosed with community-acquired pneumonia (CAP). She had been initially treated with amoxicillin-clavulanic acid, but due to poor clinical response she completed two weeks of levofloxacin. Nevertheless, after stopping levofloxacin her respiratory symptoms persisted.

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Coexistence of asthma and gastroesophageal reflux disease (GERD) is very common in older patients. GERD can cause asthma-like symptoms and asthma can exacerbate GERD by increasing intrathoracic pressure. Although this patient has long-standing severe asthma, her worsening symptoms in last 6 months with low-grade fevers is not consistent with asthma's natural history.

Based on her past medical history and her medications, this patient has no apparent underlying immunosuppression, which makes nocardiosis or pulmonary *Cryptococcus spp.* infection unlikely. Denosumab, a receptor activator for nuclear factor kappa-B ligand (RANKL) inhibitor used for the treatment of osteoporosis, has been associated with increased risk of cystitis and skin infections, but no clear pattern in the type of infections has been recognized. Without the appropriate epidemiological exposure, endemic mycosis and parasites causing Loffler syndrome can be dismissed.

The recent diagnosis of pneumonia with a non-resolving course, despite adequate treatment for the most common and atypical bacterial causes of CAP, further supports an ongoing chronic infection, such as NTMs and ABPA or non-infectious causes like eosinophilic granulomatosis with polyangiitis or malignancy. If the symptoms improved with levofloxacin but not with amoxicillin/clavulanic acid, this would be suggestive of NTM disease, as it could have been partially treated. As initial work-up, a complete blood count assessing the presence of eosinophilia and a chest x-ray would help guide our next best step.

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The white-cell count was 11,900 per cubic millimeter, with 77.1 percent granulocytes, 18.7 percent lymphocytes, 6.4 percent monocytes, and 2.8 percent eosinophils. Other laboratory values were as follows: hemoglobin, 14.7 g per deciliter; mean corpuscular volume, 91.2 fl; 290,000 platelets per cubic millimeter; serum creatinine, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, alkaline phosphatase and bilirubin were within normal range. Serum C-reactive protein was 7.43 mg/dL (normal < 0.5 mg/dL) and the erythrocyte sedimentation rate (ESR) was elevated (48 mm per hour). A chest x-ray was performed (figure 1). An echocardiogram recently performed was informed as normal.

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Although asthma is the cardinal manifestation of eosinophilic granulomatosis with polyangiitis and it can precede the rest of the vasculitic features by up to ten years, an eosinophil percentage at least above 10% is the most characteristic finding. Vasculitis or disseminated malignancy are often associated with very high inflammatory markers, with the ESR commonly above 100 mm/h, making these two entities unlikely in this cause. A negative antineutrophil cytoplasmic antibody (ANCA) would robustly exclude the former. Peripheral eosinophilia is also typically seen in ABPA, with total IgE levels usually over

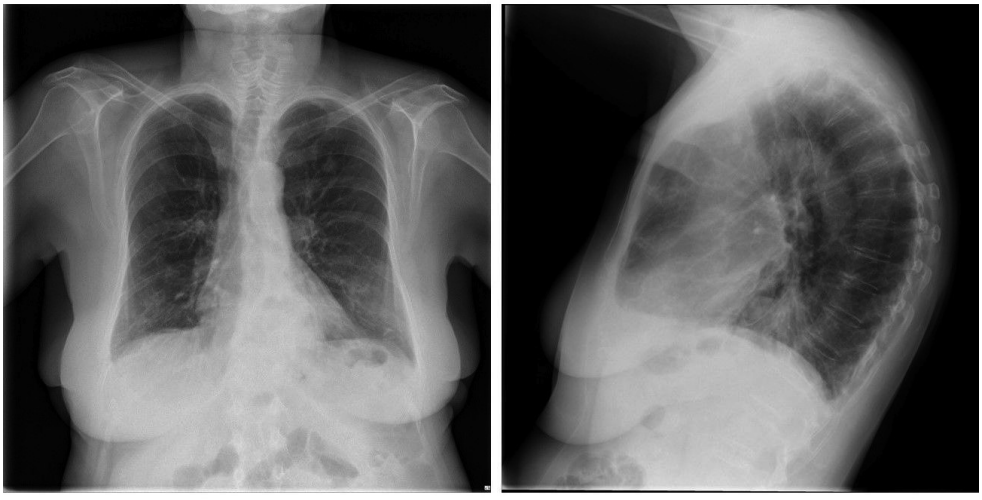

Figure 1 | **Thoracic radiography showing signs of pulmonary hyperinflation and a hiatal hernia.**

1000 UI/ml and detectable specific IgE against *Aspergillus fumigatus*.

The chest radiograph findings are also compatible with histoplasmosis. Nonetheless, almost all cases of histoplasmosis have been in immigrants or returning travellers from an endemic regions, which was not the case of this patient. Lymphangitic carcinomatosis, secondary to a bronchogenic adenocarcinoma and pulmonary NTM infection should also be considered, given the presence of a pulmonary nodule with diffuse, bilateral reticulonodular pattern.

Sputum samples should be sent for microbiological cultures, with specific stains to identify acid-fast bacilli and fungal organisms.

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Four different sputum cultures were positive for *Aspergillus fumigatus, Aspergillus niger, Aspergillus flavus* and *Aspergillus lentulus.* Three different sputum cultures were also positive for *Mycobacterium intracellulare. Stenotrophomonas maltophilia* and *Neisseria meningitidis* were also isolated in a different sputum culture sample.

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The finding of multiple sputum cultures positive for bacteria, mycobacteria and fungi at the same time might seem odd at first. However, all of these pathogens are catalase-positive organisms and are frequently isolated from patients with bronchiectasis. The catalase enzyme converts hydrogen peroxide to water and oxygen, thus protecting microorganisms from oxidative damage from reactive oxygen species (ROS). The NADPH oxidase complex, a cluster of cytosolic and membrane-bound proteins that donate an electron from NADPH to oxygen to produce superoxide, present in neutrophils and monocytes/macrophages, produce enough ROS to effectively kill microorganism that have been phagocytosed.

Chronic granulomatous disease (CGD) is a rare, primary immunodeficiency, usually x-linked (or rarely autosomal recessive), characterized by phagocytes with defective killing of the ingested microorganisms because of a deficient production of ROS by mutations in any of the five structural subunits that conform the NADPH oxidase complex. Impaired clearance of bacterial and fungal pathogens leads to recurrent infections and granulomatous inflammation, commonly involving the lungs. In addition to recurrent infections, there is ongoing dysregulated inflammation that leads to autoimmune disorders generally involving the gastrointestinal tract and the lungs.

Although, CGD can first manifest in adulthood, it would be uncommon to debut at this age especially not having a prior history of recurrent infections. Nonetheless, she could be an X-linked carrier with a dual phagocyte population due to lyonization or have a mild form of the autosomal recessive mutation and measuring NADPH oxidase activity would exclude the diagnosis.

S. maltophilia infection, a common cause of hospital-acquired pneumonia should be addressed and treated with trimethoprim-sulfamethoxazole. *N. meningitidis* rarely causes pneumonia and can be a normal colonizer of the oropharyngeal flora in around 10% of the population; treatment with ceftriaxone is justified to avoid a potentially fulminant course if left untreated. The radiological findings of pulmonary NTM infections can be protean. A chest computed tomography (CT) would be more sensitive to identify typical findings such as central bronchiectasis, tree-in-bud opacities, ground-glass opacities and scattered nodules; which in an elderly female

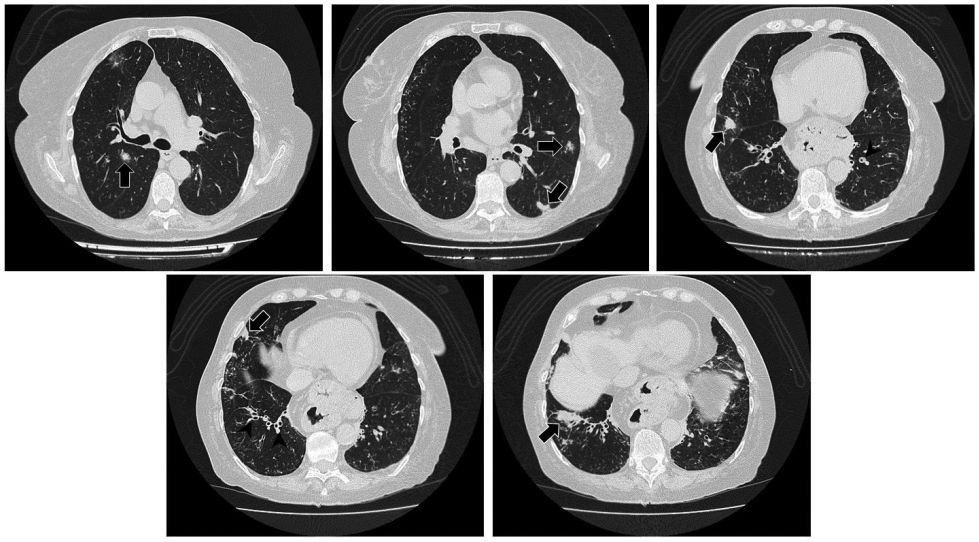

Figure 2 | **Chest computed tomography with diffuse bronchial wall thickening (arrowhead) and signs of airways disease accompanied by scattered nodular pulmonary infiltrates (arrow).**

patient is classically referred to as Lady Windermere syndrome (named after Oscar Wilde's Victorian-era play Lady Windermere's Fan, embodying the idea that expectorating is socially unacceptable in females). Tuberculosis should be ruled out whenever you think of NTM infections.

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Levofloxacin (500 mg daily for 10 days) was prescribed for *S. maltophilia*. A chest CT scan was performed (figure 2). Human immunodeficiency virus (HIV)-antibody test was negative. NADPH oxidase activity was normal in both monocytes (73%) and granulocytes (100%). Lymphocyte subsets, immunoglobulin levels and complement activity were informed as normal. Total serum immunoglobulin E (IgE) and *A. fumigatus*–specific IgE antibodies levels were normal (11.70 KU/l [≤120.00] and 0.10 KUA/l [<0.35], respectively). Serum galactomannan antigen was negative. The *Mycobacterium intracellulare* susceptibility test results were received. It resulted susceptible to clarithromycin and resistant to rifampicin, ethambutol, isoniazide, linezolid, pyrazinamide, and streptomycin.

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Normal immunoglobulin levels and complement activity make common variable immunodeficiency disease or complement deficiencies unlikely. CGD, HIV and ABPA have also been ruled out. As shown in this case, patients presenting with chronic, pauci-symptomatic infections should always have more specialized imaging performed. The CT findings seen with bronchiectasis and diffuse tree-in-bud opacities are characteristic of pulmonary *M. intracellulare*. However, there are also two nodules with surrounding ground-glass opacity (halo sign), an early sign aspergillus's infection, that a normal galactomannan antigen level would not rule out. Due to the possibility of pulmonary *Aspergillus* infection, treatment with voriconazole should be started.

It is challenging to discern the relative contribution of each pathogen isolated towards the patients' symptoms. A first step would be to determine the patient's response to levofloxacin. Although this patient presumptively meets microbiological ATS/IDSA diagnostic criteria for pulmonary *M. intracellulare* infection, it rarely requires urgent treatment. Due to the voriconazole-rifampin interaction and the presence of another concomitant infection, postponing its treatment for now, seems reasonable.

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The patient did not fulfill the Infectious Diseases Society of America (IDSA) criteria for lung disease by nontuberculous mycobacteria at this point because other diagnosis could not be ruled out (*Aspergillus* could not be dismissed as responsible for the lung nodules). Simultaneous treatment with voriconazole and rifampicin was considered to be contraindicated. It was reasoned that antifungal treatment would be shorter than nontuberculous mycobacterial treatment. Thus, voriconazole was started. Influenza vaccine and pneumococcal conjugate and polysaccharide vaccines were recommended. After six weeks of treatment, voriconazole was stopped. The patient had regained 1 kg weight, but still maintained a mild persistent non-productive cough. A new chest CT

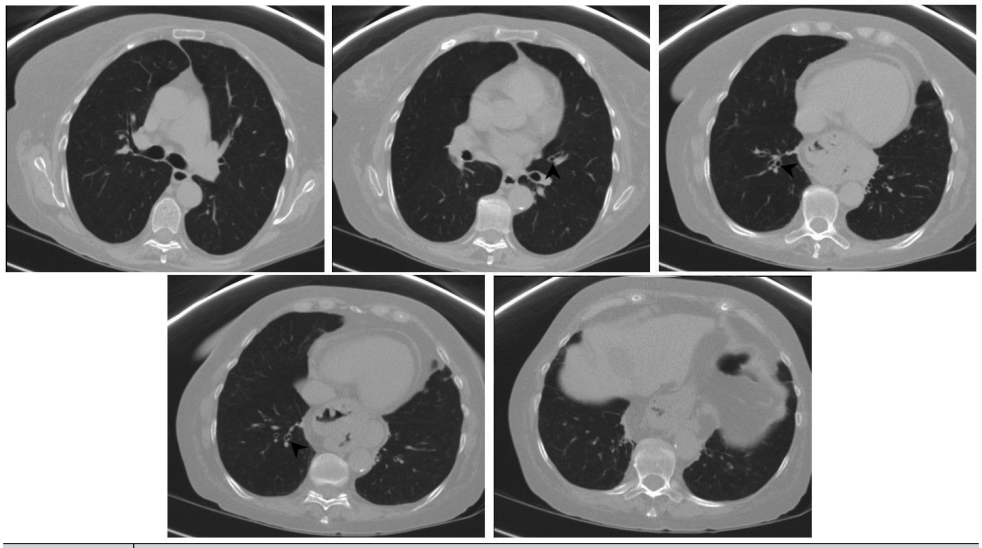

Figure 3 | **Chest computed tomography at the end of treatment for *Aspergillus* spp, showing radiological resolution of the pulmonary parenchymal infiltrates but persistent features of airways disease and bronchial wall thickening (arrowhead).**

showed radiological resolution of the parenchymal infiltrates consistent with improvement of the signs of the inflammatory airway disease (figure 3).

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First, we must reiterate that *M. intracellulare* infection is seldom a condition that merits urgent therapy and other potential diseases must be ruled out and treated beforehand. Prior radiological and microbiological findings, along with response to treatment with voriconazole is consistent with pulmonary aspergillosis.

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Due to the clinical and radiological improvement, it was decided to postpone the *M. intracellulare* treatment. Nevertheless, two months later, the patient attended the outpatient clinic complaining of asthenia, persistent productive cough and moderate dyspnea, which had progressively worsened in the previous weeks. *M. intracellulare* was again isolated in sputum cultures. The culture of sputum for fungi was negative. A new chest x-ray was reported to be normal.

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This patient fulfills ATS/IDSA diagnostic criteria of pulmonary *M. intracellulare* infection, with ongoing characteristic clinical manifestations, persistent microbiological isolation and compatible radiological signs. Chest x-ray often misses the typical radiological pattern associated with Lady Windermere syndrome; thus, a chest CT is warranted to both confirm its presence and serve as baseline test for future monitoring.

Treatment with a macrolide, rifampin and ethambutol should be started. Macrolides are the backbone of therapy, with ethambutol and rifampin used to avoid development of resistance against them. Only macrolides have shown correlation between *in vitro* susceptibility and clinical response, thus *in vitro* minimum inhibitory concentrations of the other drugs reported as resistant, should not be excluded from the drug regimen. In the absence of cavitary lesions thrice-weekly dosing could be offered, as it is usually better tolerated. Pulmonary function test (PFTs) should also be performed to objectively evaluate the impact of the disease over the patient's lung capacity.

A prolonged course of therapy (i.e. 12-18 months) with repeat sputum cultures to document microbiological clearance, chest imaging to evaluate resolution of parenchymal involvement and PFTs are usually required. Drug toxicity monitoring and dose adjustment based on clinical parameters, tolerance and pharmacological interactions should be done throughout the treatment course. Joint care by a pulmonary and an infectious disease physician offers the best chance of clinical improvement and cure. Given the unmodifiable, underlying anatomical predisposing factor (i.e. bronchiectasis), clinical symptoms and repeat imaging commonly waxes and wanes over the course of treatment, with often complex clinical decision.

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It was considered that the role of *M. intracellulare* was more prominent than previously thought and treatment for this infection was started. According to IDSA recommendations, daily treatment with clarithromycin (500 mg), rifampicin (600 mg daily) and ethambutol (1,200 mg) was started, in spite of reported resistance to rifampicin and ethambutol. Treatment was well tolerated and no side effects were reported. The patient had an important improvement in her general fitness, and the cough completely resolved. She was able to resume social activities and after twelve months the treatment was stopped. Six months after stopping the treatment, the patient remains asymptomatic and is periodically being followed as an outpatient.

DISCUSSION

This previously active old woman presented with both subacute pulmonary and systemic symptoms. The simultaneous isolation in sputum of different bacteria, mycobacteria and moulds was initially perplexing.

S. maltophila and *N. meningitidis* were considered as easy to treat *innocent bystanders*. Nevertheless, superinfection by conventional bacteria was described in both fungal and mycobacterium lung diseases [1,2].

The most challenging finding was the presence of bilateral pulmonary nodular opacities that could be attributed to both *Aspergillus* and *M. intracellulare* infection. The clinical presentation of *Aspergillus* lung disease oscillates from ABPA to invasive pulmonary aspergillosis (IPA), and includes intermediate forms such as chronic pulmonary aspergillosis (CPA) and subacute IPA. Isolation of *Aspergillus* in respiratory samples is part of their diagnostic criteria [3-5].

Despite her previous diagnosis of asthma, the patient did not fulfill criteria for ABPA since neither total nor *A. fumigatus*-specific IgE antibodies levels were elevated [6]. Moreover, the absolute number of eosinophils was in the normal range. She did not present any of the risk factors associated to IPA like neutropenia or dysfunction of cellular immunity [5,7] and none of the typical radiological lung lesions associated to IPA were identified [5].

Recently, an uncommon but potentially severe form of fungal infection called CPA was described [1]. CPA complicates many respiratory disorders in non-immunosuppressed patients. Diagnosis depends on the isolation of the mould in respiratory samples, a CT lung scan with one or more nodules of different sizes and irregular borders that may be cavitated, response to treatment and/or histological confirmation. The differential diagnosis is broad and includes tuberculomas, lung carcinoma, coccidioidomycosis, histoplasmosis, blastomycosis, actynomicosis or rheumatoid nodules [1].

NTM lung infection is an underlying condition associated to CPA [8,9]. In a study which included 566 patients with a previous diagnosis of NTM lung disease, CPA was detected during follow-up in 7.2% of subjects. Coinfection by both microorganisms presented a significative increase in mortality (19.5% vs. 1.7%; $p < 0.001$) [8].

Diagnosis of NTM lung disease can be stablished in a patient with NTM isolation in at least two different respiratory samples and the presence of compatible lung radiological lesions (multifocal bronchiectasis and multiple small nodules) [2]. Our patient fulfilled all criteria except one, which is exclusion of other diagnoses. Strikingly, our case was notable for the presence of many of the features associated to Lady Windermere syndrome: she was a tall, lean, non-smoker, old woman with hyperkyphosis presenting with chronic cough [10,11].

The decision to initially treat the fungal infection was based on two factors: first, the hindrance to simultaneously prescribe an azole and a rifamycin; second, treatment of NMT infection would require a much longer period of time (delaying the treatment of the *Aspergillus* for many months).

The diagnosis of a nodular type of CPA was finally confirmed by the remarkable disappearance of the nodules under antifungal treatment, albeit treatment was shorter than usually recommended.

Treatment of NTM infection was deferred due to the marked clinical improvement under voriconazole. Treatment was later started when her respiratory symptoms recurred. She presented a striking sustained improvement afterwards.

The prominent hiatal hernia observed in the chest CT deserves a comment as it may have played a cornerstone role. Hiatal hernia is a well-known risk factor for GERD [12]. GERD has been associated to recurrent episodes of microaspiration that have been linked to lung inflammation leading to asthma, bronchitis and pneumonia. GERD was found in 44.2% of patients with NTM lung disease vs. 27.6% of controls ($p=0.02$) [13]. A registry of 1,826 patients with non-cystic-fibrosis bronchiectasis observed that GERD was significantly more frequent in those with NTM lung disease than in those with bronchiectasis related to other entities (51% vs. 40%, $p<0.01$) [14].

Possibly, the chain of events is as follows: hiatal hernia, GERD, NTM lung disease, chronic nodular aspergillosis and common bacterial superinfection.

Even though *Aspergillus* is a ubiquitous fungus in nature, its isolation should not be underestimated in respiratory samples of non-immunocompromised patients with a previous diagnosis of a chronic pulmonary disease (including NTM lung infection). Patients with simultaneous isolation of potentially life-threaten microorganisms deserve a step by step approach to make decisions based on the clinical and radiological features in conjunction with the potential side effects of the drugs available for treatment.

CLINICAL TEACHING POINTS

1.- Tall and lean old woman with hyperkyphosis presenting with chronic cough and repetitive isolation of non-tuberculous mycobacteria in sputum samples should be considered for Lady Windermere syndrome

2.- Isolation of *Aspergillus* in respiratory samples should not be underestimated in apparently non-immunocompromised patients presenting with chronic lung diseases

3.- Hiatal hernia and gastroesophageal reflux disease should be considered as predisposing factors for the developing of asthma and other types of chronic lung diseases

4.- Physicians should cautiously design treatment regimens of infections that require the administration of drugs that should not be used simultaneously, as voriconazole and rifampicin

5.- A stepwise approach should be considered when the superimposable clinical and radiological manifestations can be produced by different microorganisms isolated in a single sample, as was a mycobacterium and a filamentous fungus in this patient

FINAL DIAGNOSIS

Pulmonary infection by *Mycobacterium intracellulare* (Lady Windermere syndrome) with invasive pulmonary aspergillosis as a superinfection.

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None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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