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A patient with a rapidly lethal pneumonia after a visit to a touristic area in rural Leon (Spain)

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PRESENTATION OF CASE (DR. MARICELA VALERIO)

A 60 year old lady, presented to the Emergency Department of Hospital General Universitario Gregorio Marañón (HGUGM) in Madrid in November 2017 with a 4 day history of malaise, fever, chest pain and dyspnea.

She had a left side breast cancer in 2001 that received treatment with surgical resection of the nodule, axillary lymphadenectomy, chemotherapy, local radiotherapy and finally, hormonal therapy with tamoxifen for 5 years and letrozol for 2 years. She had no recent evidence of recurrence.

She was a smoker until several years ago, when she quit smoking and did not report any drug allergy or to other products. She had no underlying heart disease and was not receiving, regularly, drugs of any kind. She had never travel out of Spain. She had not been vaccinated recently.

Six days before her admission she had a family touristic trip to an area in the North West of Spain called Las Médulas, an historical roman gold mining area in the province of León. She entered several caves and tunnels but denied any contact with animals or birds, including bats and no particular exposure to dust. She denied eating uncooked products or unpasteurized milk or cheese.

During the trip, she started with fever, malaise and headache, and decided to prematurely return to Madrid and stayed at her home with symptomatic treatment, 4 days later she began with dry cough and dyspnea. Due to the rapid deterioration of her clinical condition she went to the Emergency Department (Day 0). On admission she had dyspnea, tachypnea, tachycardia and hypotension, blood cultures were obtained and IV fluids and antibiotic treatment with ceftriaxone (2 g IV q.d.) and levofloxacin (750 mg q.d.) was administered before her transfer to the Intensive Care Unit.

A chest X-ray taken on admission is shown in figure 1. Radiologic report states that "there is an Upper Right Lobe (URL) consolidation with potential amputation of the superior URL bronchus. Increased density in the right lung hilum. Possible pneumonia. A central hilum tumor should be ruled out".

Other complementary data obtained on admission were the following: hemoglobin 12.7 g/dL, hematocrit value 35.9 %, mean corpuscular volume 93.2 fL, platelet count 170,000 uL, white blood count 6,800/uL (neutrophils 6,200 uL, lymphocytes 400 uL, monocytes 10 uL, eosinophils 300 uL). Prothrombin time 25.5 sec, I.N.R. 2.11, fibrinogen >1000 mg/dL, A.P.T.T. 35.8 sec.

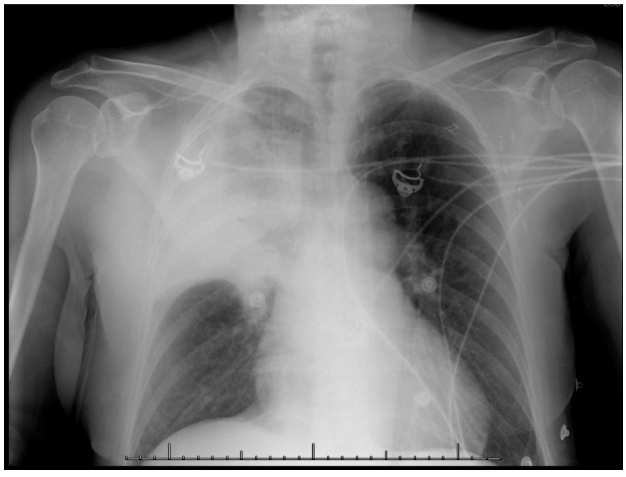

Figure 1 | **Day of admission**

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Venous blood data: pH 7.43, pCO_2 34 mmHg, pO_2 28 mmHg, O_2 saturation of 55 %, HCO_3 23 mmol/L, BEb -1.2 mmol/L, lactate of 5.0 mmol/L, glucose 107 mg/dL, ALT 46 U/L, total billirubin 1.2 mg/dL, GGT 19 U/L, alkaline phosphatase 49 U/L, CK 47 U/L, amilase 18 U/L, lipase 15 U/L, creatinine 1.03 mg/dL, glomerular filtrate 55 mL/min/1.73 m^2, Na 139 mmol/L, K 3.6 mmol/L, Cl 99 mmol/L, Ca 8.5 mg/dL. troponin T 6 ng/L , Nt-proBNP 5,204 ng/L, PCR 34.0 mg/dL, PCT 8.39 µg/L. Normal ECG.

ICU admission. Due to shock and progressive hypoxia (O_2 sat 91%) despite 100% ventimask and noradrenalin, she was transferred to the ICU. At the time of ICU admission she was conscious and mentally oriented with a Glasgow coma score of 15. The patient had sinus tachycardia. No heart murmurs were present. Abdomen was soft with no liver nor spleen enlargement. There was a discrete abdominal pain on palpation of the right hipocondrium. No signs of peritoneal irritation were present. No peripheral edema nor signs of deep venous thrombosis were present. Peripheral arteries pulsed symmetrically.

Legionella antigenuria was informed as negative and *Streptococcus pneumoniae* antigenuria as positive.

Day +2 after admission. A progressive deterioration of the respiratory function occurs and oro-tracheal intubation was required (Figure 2 Chest X ray). Persistent desaturation down to 75% occurred despite FiO_2 of 100% and PEEP of +18mmHg. Vasoactive drugs needs increased (adrenaline and noradrenaline) and a new right bundle block became evident in the urgently performed EKG. A trans-thoracic echocardiogram (TTE) revealed an important dilatation of the right ventricle with severely depressed function.

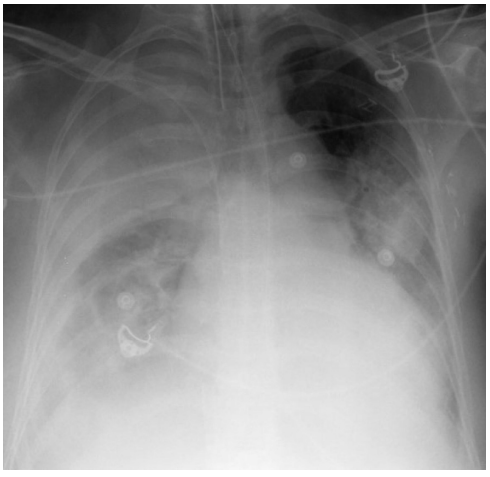

Figure 2 | **Day +2 after admission**

Day +3 to +6 after admission. An evolution to multi-organic failure occurred and blood cultures remained negative. Massive pulmonary thromboembolism was suspected and thrombolysis with alteplasa was performed. The patient required ECMO and continuous veno-venous hemofiltration (CVVHF) due to oliguric renal failure. On day +5 a fiberoptic bronchoscopy showed a permeable bronchial tree, with normal mucosa and no active bleeding. Samples for culture were obtained and antimicrobial treatment was modified, including now meropenem, vancomycin, and clindamycin.

A new TTE showed a severely dilated and severely dysfunctional right ventricle, with moderate-severe tricuspid valve dysfunction and a minimal pericardial fluid.

Consumption coagulopathy persisted despite the administration of vitamin K and progressive anemia and thrombocytopenia develops. Cultures taken during fiber optic bronchoscopy were all negative.

Complementary data requested include: Negative AVH, BVH, CVH, VIH, Rose of Bengal, *Rickettsia*, *Borrelia*, *Legionella*, *Mycoplasma*, *Coxiella*, *Chlamydia*, *Leptospira, Cryptococcal antigen* and *Aspergillus antigen.*

Blood PCR for *Bartonella and Coxiella burnetii* were both negative. The *Plasmodium antigen* was also negative and no microorganisms were seen in Giemsa stains of peripheral blood samples. CMV and EBV viremia were negative.

Other negative respiratory samples included: RSV, Influenza A and B.

Day +7 after admission. An abdominal echocardiogram showed: Enlarged liver (Up to 19 cm) of homogenous parenchyma. Normal biliary tree. Spleen-portal axis and pancreas were unremarkable as were both kidneys and the excretory system. Minimal pleural fluid and ascitic fluid were detected. CT scan could not be performed due to the critical and unstable situation of the patient.

Final evolution. The patient died on day +10th of admission and a limited, echography guided autopsy, was authorized by the family.

DIFFERENTIAL DIAGNOSIS (DR. FRANCISCO LÓPEZ-MEDRANO)

Thank you very much for inviting me to discuss this clinical case. I am totally unaware of the final diagnosis of the case. Three important factors have to be considered for the final approach to the diagnosis of a potential infectious disease: the clinical manifestations and syndromic diagnosis, the time of evolution and the risk factors of the patient. Those three aspects for this patient are, in my opinion: pneumonia, of acute evolution after a visit to an historical, not active, mining roman area in Leon, Spain.

Regarding the first aspect, the patient is a 60 year old

lady, apparently immunocompetent, that develops a rapidly evolving febrile disease with pulmonary infiltrates and a positive urine test for pneumococcal antigen. Here we may have, in my opinion, three potential scenarios. First, we are assisting to an episode of fulminant pneumococcal pneumonia affecting an immunosuppressed patient, second, we have a false positive pneumococcal antigenuria and there is an alernative etiology for the pneumonia or, finally, this is an episode of pneumococcal pneumonia with co-infection with another microorganism. In a recent article by Sanges et al [1], patients 18 to 40 year-old who had experienced an invasive infection with encapsulated bacteria were examined searching for primary immunodeficiencies (PIDs). Out of 36 such cases, 7 (19%) had a PID which included idiopathic primary immunodeficiency and hypogammaglobulinemia and also complement (C6 and C7) deficiencies. Authors concluded that PID screening should be considered after a first unexplained invasive encapsulated-bacteria infection in young adults.

Regarding the issue of pneumococcal antigen present in this patient's urine, Couturier et al [2] review the literature to that time and showed specificities of the test, generally from 90-100% with only occasional exceptions. My consideration is that this test is credible in this patient and very significant for my final diagnosis.

However, due to its fulminant course, we should consider other potentially treatable alternatives. We have to consider, either virus, bacteria, mycobacteria, fungi or parasites. Chapter 69 of the 2014 edition of Mandell's textbook of Infectious Diseases, written by Ellison and Donowitz [3], lists in several tables, common and uncommon causes of acute pneumonia, but we have to try to reduce the size of this long list to maintain only those etiologies that best fit with the case from a clinical, radiological and epidemiological point of view. Influenza and Respiratory Syncytial Virus heads the list of common viral agents, *S. pneumoniae* is the main cause of bacterial infections and Histoplasma the most common cause of fungal pneumonia, particularly after visiting caves. When considering specifically the main causes of non-resolving pneumonia, *Yersinia pestis*, *Burkholderia pseudomallei, Hantavirus* sp., *Coccidiodes immitis, Blastomyces* sp., *Histoplasma* sp. *and Cryptococcus gattii* are among the most commonly listed agents. Many of these agents are easily eliminated on the basis of epidemiological conditions and patient's history. *Cryptococcus gattii* has been reported occasionally in Spain [4] and *Strongyloides stercoralis* has been also diagnosed in autochthonous Spanish populations (Valencia and Alicante, but not in León) [5]. Hantaviruses are the etiological agents of hemorrhagic fever with renal syndrome in Europe and Asia, and hantavirus pulmonary syndrome is mainly an American entity. There is seropositiviy to Puumala, Hantaan and Seoul virus only in a low proportion of persons in some regions of Spain [6, 7] but cases with pulmonary involvement have been never described in Spain and the diagnosis of Hantavirus is highly improbable in this lady. Regarding the area of the patients visit we were not able to find any suggestive entity compatible with this case even when *Francisella tularensis* was reported in vole populations in that part of Spain [8] and has been described in outbreaks in the past [9-12].

My final consideration is the possibility of having a pneumococcal pneumonia and "something else".

In a review of the etiology of community-acquired pneumonia in the USA, reported by Jain et al [13], a bacterial and viral coinfection was demonstrated in 3% of the episodes. One virus of interest is adenovirus [14] that may occur in patients with no prior underlying condition. The same may occur with HSV in previously normal hosts that are able to cause a severe, non-resolving pneumonia in immunocompetent patients [15]. Bouza et al, reported Herpes simplex as a cause of worse prognosis when present in patients with ventilator-associated pneumonia [16].

Dr. López Medrano Diagnosis

My presumptive diagnosis is then: fulminant pneumococcal pneumonia due to co-infection with Herpes simplex virus or Adenovirus.

EVOLUTION OF THIS PATIENT (DR. MARICELA VALERIO)

In the final days of the life of the patient, or immediately after her death, the results of other requested tests were reported. Blood PCR test for Hantavirus and *C. burnetii* were reported negative and a blood test for *Histoplasma* spp. was also negative. Bacterial cultures of the bronchoalveolar lavage (BAL) samples were negative but a PCR test amplified *S. pneumoniae*. In the lung samples obtained by transthoracic biopsy after death, PCR was also positive for *S. pneumoniae*.

The liver and kidney echography guided biopsies obtained postmortem were negative by culture and PCR negative also.

Pathology reported changes compatible with disseminated intravascular coagulation. Bone marrow biopsy was

Table 1 Lymphocyte populations

	Percentage	Normal range (%)	Absolute value (cells/µL)	Normal range (cells/µL)
T cells (CD3+)	68%	55-82	191	700-2100
T cells (CD3+ CD4+)	37%	28-57	107	300-1400
T cells (CD3+ CD8+)	30%	10-39	87	200-1200
Coeficient CD4/CD8	1.2	1-3.6		
B cells (CD19+)	24%	6-19	65	100-500
LGL/NK cells (CD3-/ CD56+)	6%	7-31	16	90-600

hypo-cellular with marked decrease of megakaryocytic and granulocytic series and a relative increase in the red blood cell series, with dyserythropoiesis. Findings were interpreted as compatible with sepsis, disseminated intravascular coagulation (DIC), and haemophagocytosis.

The Immunology Laboratory reported: anti-cardiolipin IgG and IgM, Anti-Beta 2 GPI IgG and IgM, native Anti-DNA and Antinuclear antibodies, all negative. Immuneprotein levels in serum were reported as follows: IgG 893.0 mg/dL (normal range: 650-1610), IgA 221.0 mg/dL (normal range 90-497), IgM 123.0 mg/dL (normal range 42-255). Other serum values included complement C3 57.7mg/dL (normal range 91-190), C4 14.4mg/dL (normal range 18-56) and C-reactive protein 18.4mg/dL (normal range 0-0.8). Figures of different lymphocytic populations were clearly decreased and are summarized in table 1.

FINAL DISCUSSION

Several points of the presentation and evolution of this case deserve discussion, in our opinion.

First of all, the patient had, among the early laboratory tests, a positive pneumococcal antigen in urine. Determination of pneumococcal antigen in urine, is recommended by IDSA in patients with pneumonia that require ICU admission, those who fail response to the initial antibiotic treatment, patients with low white blood count, alcoholics and patients with pleural effusion and asplenia [17]. Sensitivity and specifcity of this test vary depending on different circumstances. Blaschke et al reported [18], sensitivities with the Binax NOW test from 70 to 90 % with specificities from 80 to 100% in adults with pneumonia. Results may be worse in patients who are nasopharyngeal carriers of *S. pneumoniae* and better in patients with severe infection and bacteremic pneumococcal pneumonia [19-21].

Another question in this case, is the interpretation of a specific PCR for *S. pneumoniae*, both in lower respiratory tract samples obtained by BAL and in lung biopsies postmortem. Sensitivity is considered variable but specificity could be superior to 95% according to different authors [22-25].

The reasons for the very aggressive behavior of pneumococcal infection in this patient, remain obscure for us. Fulminant pneumococcal infection is an uncommon but well known situation, particularly in immunocompromised and asplenic patients, either traumatic or functional [26-37]. However, it can also occur in non-immunocompromised subjects by mechanisms that are not totally clarified [38]. We could not demonstrate a situation of functional asplenia in our patient and only speculated with the potential radiation of the spleen while she received radiotherapy for her left breast cancer, several years before.

This patient, had very low figures of serum complement, that have also been associated with a risk of poor evolution in patients with pneumococcal infection [39-43]. Hypocomplementemia may be in the origin of the evolution of this patient, but in our opinion, it is the consequence of sepsis and DIC [44]. A previous report suggested that pneumococcal capsular polysaccharides (PCPs) were responsible for initiating DIC through inflammation induced by PCPs, per se, or an antigen–antibody reaction [45]. Also, certain serotypes of *S. pneumoniae* may be particularly invasive [46] but not having an isolate, we were unable to serotype this case.

Another probable diagnosis that needs to be mentioned, is the hemophagocytic syndrome secondary to the infection. The most common infectious trigger of this syndrome are viral infections. Bacterial causes are less common but cases of *S. pneumoniae* infection related hemophagocytic syndrome have been described [47, 48]. Hemophagocytic syndrome could be diagnosed if at least 5 out of 8 criteria are present, our patient only met 4 of them (fever, hypofibrinogenemia, hemophagocytosis and bicitopenia) but ferritin concentrations, CD25 levels and cytotoxic activity of NK cells were not determined [49].

Finally, we were surprised by the severe cardiovascular events of this patient. It is known that patients hospitalized for pneumococcal pneumonia have a higher risk of cardiovascular events than similar populations. Complications include, acute myocardial infarction, auricular fibrillation, ventricular tachycardia and acute heart failure [50-54]. Most commonly, those events occur very early in the natural history of pneumococcal infection with 55% of them reported in the very first day of admission, with a progressive decrease in the following month. Musher et al [55] found 33 cardiovascular severe events in a population of 170 cases admitted with pneumococcal pneumonia. A national retrospective cohort of patients with pneumococcal pneumonia in Taiwan was compared with a similar population without pneumonia, and the authors showed a higher risk of thromboembolic episodes (deep venous thrombosis and puylmonary emnbolisms) in the population with pneumonia, particularly within the first four weeks of evolution [56].

This patient had never received a pneumococcal vaccine, and our speculation in the discussion of the case was if vaccination could have avoided this episode or at least decreased its severity and preserve patient's life.

FINAL DIAGNOSIS

Invasive pneumococcal infection with pneumonia and fulminant sepsis.

Disseminated intravascular coagulation.

Right heart failure probably due to pulmonary embolism.

Hypocomplementemia and lypmphopenia

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None to declare.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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