A case of hemolytic anemia associated with interstitial lung disease, arthralgia and fever caused by *Mycoplasma pneumoniae*

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ABSTRACT

Pulmonary interstitiopathies became the most diagnosed forms of pneumonia in 2020 due to the coronavirus (COVID-19) pandemic. The spectrum of interstitiopathies is broad and includes idiopathic diseases and secondary forms. In April 2020, a 36-year-old man was admitted to our department for arthralgias, fever, asthenia, cough, and dyspnea. In January 2020, fever, cough, arthralgias, and asthenia appeared. In April, his general condition worsened with the development of macrohematuria, malaise, and intense asthenia. On admission, the patient presented pale, asthenic, and symptomatic for dyspnea and arthralgias. There was objective joint pain in the small joints of the hands, elbow, and knees with morning stiffness and decreased strength. Computed tomography of the chest documented ground-glass opacities in both lung fields. He performed 2 swabs for severe acute respiratory syndrome-related coronavirus 2, which were negative. On hematochemical examination: immunoglobulin (IgM) 332 mg/dL and ferritin 700.2 ng/mL. At venous blood smear peripheral venous blood, agglutination of erythrocytes. The serology (IgM) for *Mycoplasma pneumoniae* was positive with agglutinins in the serum; doxaciclina was started. There was a progressive normalization of hemoglobin levels, cold agglutinins were gradually reduced and were no longer detected at 15 days after the start of treatment. At one month after discharge, pulmonary function had fully recovered, and the picture of hemolytic anemia was resolved.

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Introduction

The interstitial lung diseases (ILDs) are a heterogeneous group of disorders classified together because of similar clinical manifestations and imaging findings.[1] ILDs spectrum is broad and includes idiopathic and secondary forms. The development of secondary ILDs can be associated with a broad range of systemic diseases (rheumatic diseases, uremia, a congenital inborn error of metabolism), exposures to inhaled inorganic and organic dust, infectious agents, and drugs. Correct diagnosis is fundamental, and the treatment choices and prognosis are different among all the different types of ILD. Interstitial lung disease became the most diagnosed type of lung disease in 2020 because of the eruption of coronavirus 2019 (COVID-19) as a breakthrough of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) in Wuhan.[2] Since then, there has been an important shift in epidemiology, etiology, and outcome of ILDs.

Here we report a really uncommon case of a young man with cough, fatigue, fever, and arthralgia.

Case Report

In April 2020, a 34-year-old Caucasian man was admitted to our ward because of arthralgia, fever, fa-

tigue, cough, and dyspnea. The patient had been well until January 2020 when suddenly appeared high-grade fever, cough, arthralgia, fatigue. His general practitioner prescribed some laboratory tests with normal results. Acetaminophen and some course of antibiotic therapy (penicillin) were administered with slight improvement. In April, his general condition fell, and he developed dark urine, malaise, intense fatigue, and a new flare of fever, chills, and productive cough. He presented to our hospital. On admission, the patient was pale, asthenic and was symptomatic for dyspnea and arthralgias. Joint pain of the small joints of the hands, wrist, and knees was present, along with morning stiffness and decreased grip strength. Past clinical history was negative. Upon physical examination, blood pressure was 110/70 mmHg, pulse rate was 100/minute, respiratory rate was 22 breaths/min, and the temperature was 38.7°C. Chest examination showed bilateral fine, moist rales and sporadic dry rales. Chest X-ray revealed opacity in bilateral lower lobes, while abdominal ultrasound was normal. Lung computed tomographic (CT) scan revealed mediastinal and hilar lymphadenopathy, diffuse centrilobular micronodules, and patchy opacities in both lung fields with mild thickening of bronchial walls. In suspect of COVID-19, he was tested with two consecutive nasopharyngeal swab tests (polymerase chain reaction, confirming SARS-CoV-2 infection), but tests were negative. Laboratory testing is reported in Table 1. Liver profile, kidney profile, and coagulation studies were within normal limits. Serum electrophoresis revealed no abnormalities. Serum C3, C4, and total IgA and IgG levels were normal, where IgM was 332 mg/dL. Ferritin levels were 700.2 ng/mL. Microscopic examination of the peripheral blood smear (Figure 1) revealed red cell agglutination. Direct Coombs test and cold agglutinins were positive. Additionally, ANA, ANCA, ENA, rheumatoid factor, anti-HIV, anti-hepatitis B virus, anti-hepatitis C virus, Epstein Barr virus, Cytomegalovirus, and Parvovirus B19 were absent. *Mycoplasma pneumoniae* serology was positive, with specific immunoglobulin M detected in serum samples.

When the diagnosis of *M. pneumoniae* infection was established, he was also started on doxycycline. Hemoglobin levels gradually normalized. Cold agglutinins gradually decreased and are not more detected within 15 days. One month after hospital discharge, pulmonary function was fully recovered.

Discussion

Landsteiner first described cold agglutinins in 1903.[3-6] Their pathological action against red blood cells and blood vessels was later described by Clough and Iwai.[7,8] In 1953 Schubothe called this disease *cold agglutinin disease* (CAD).[9]

M. pneumoniae causes up to 40% of cases of community-acquired pneumonia and as many as 18% of

Table 1. Laboratory parameters of the patient.

	Lab parameters in the prodromic phase of the disease	Lab parameters during recovery				Lab parameters at the end of therapy
	1.31.2020	**4.4.2020**	**4.9.2020**	**4.13.2020**	**4.15.2020**	**4.30.2020**
WBC (×10³/mmc)	5280	17,700	4610	3580	3740	4980
Lymphocytes (cells/mmc)	1810	13,700	2100	1680	1870	1630
Neutrophils (cells/mmc)	2700	2700	1820	1420	1310	2460
Monocytes (cells/mmc)	460	1190	400	270	300	350
Eosinophils (cells/mmc)	250	90	250	210	240	380
Basophils (cells/mmc)	60	20	40	0	10	60
RBC (×10³/mmc)	5,710,000	2,860,000	2,910,000	1,690,000	3,740,000	5,220,000
Hemoglobin (g/dL)	16.1	10.4	9.62	11.5	12.2	15.6
Hematocrit (%)	48.8	23.9	25.5	14.5	35.1	46.9
MCV (fL)	85.4	83.7	87.6	85.9	90.8	89.9
Reticulocytes (%)	-	-	8.3%	12%	13%	-
RDW (%)	11.6	15	16.8	16.2	16.6	14.1
PLT (×10³/mmc)	224,000	651,000	272,000	272,000	224,000	278,000
LDH	-	464	-		173	-

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; RDW, red blood cells distribution width; PLT, platelets; LDH, lactate dehydrogenase.

cases requiring hospitalization in children. About 25% of patients may experience extrapulmonary complications. Autoimmune reactions have been suggested to be responsible for many of these manifestations. CAD is characterized by an auto-antibody[10] that can agglutinate red blood cells (RBCs) at temperatures lower than that of the body and subsequently activate the complement system responsible for the lysis of RBCs.

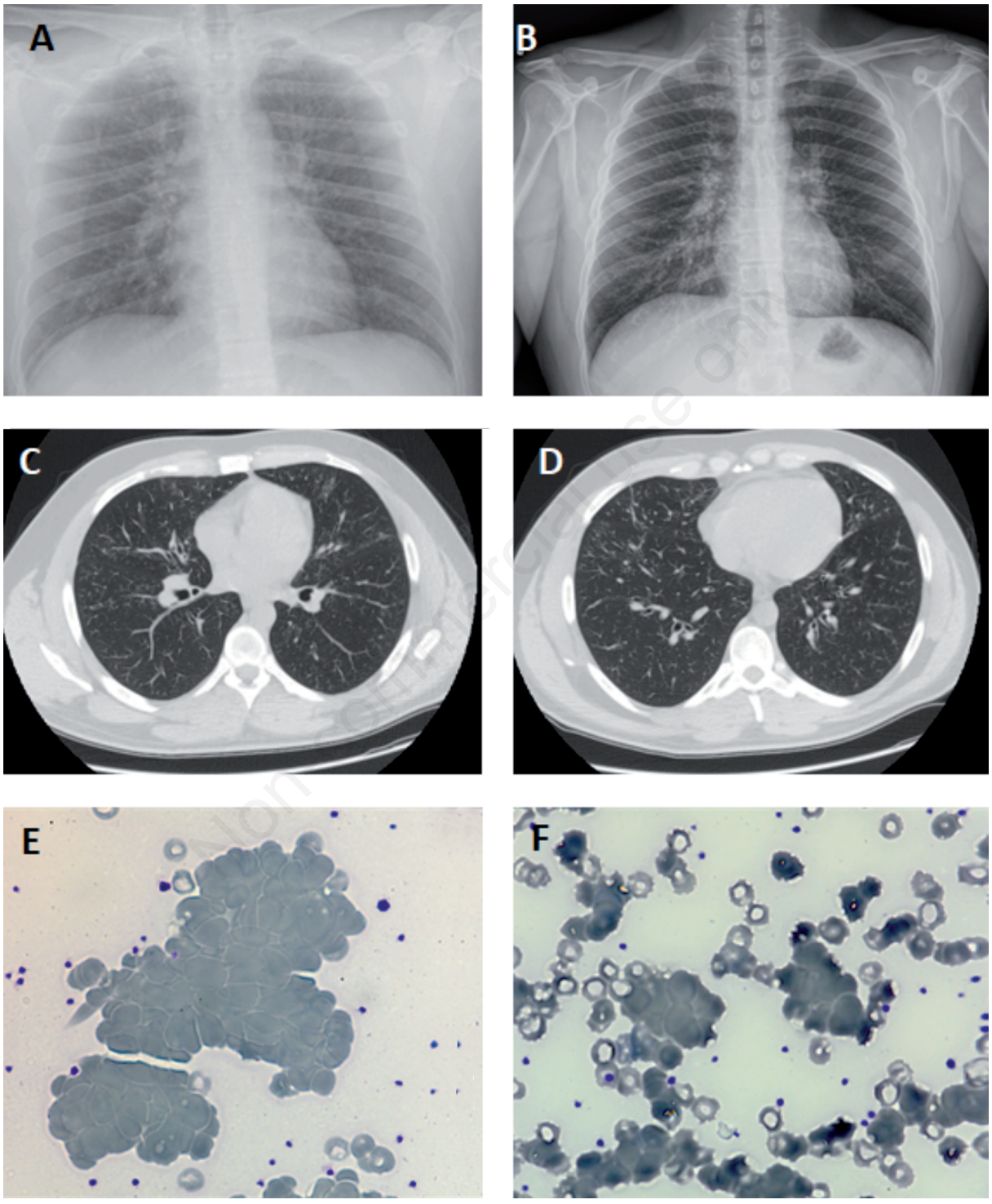

Figure 1. Chest X-ray of the patient. A) Small opacity in right upper lung and large dense opacity in the left lung on day 4 after onset. B) Chest X-ray after therapy with clear lung field on day 27. C and D) Computed tomography scan showed Bilateral opacities progressed with left lung consolidation on day 7. E and F) Blood smear showed red cell agglutination. E: 4°C image of blood smear showed agglutination of red blood cells (RBC); and F) at 37°C showed normal distribution of RBC.

Cold agglutinin antibodies are mainly specific for the RBCs membrane systems,[11] and their production can be stimulated by *M. pneumonia* or by lymphoproliferative disorders. The auto-antibody involved is usually an IgM, which can agglutinate RBCs at temperatures of between 0 and 5°C. Complement activation generally occurs between 20 and 25°C but is also possible at normal body temperature. Hemolytic anemia is recognized as a rare but severe complication of Mycoplasma infection. Our patient presented with anemia due to intravascular hemolysis accompanied by articular involvement. This particular effect has been described previously with infections by *Mycoplasma* (also known as *hemoplasma* in this setting) via induction of complement receptor 1 expression on erythrocytes.[3] Complement receptor 1 mediates immune adherence, a fundamental event for destroying microbes and initiating immunological responses. Hemoplasma determines hemolytic anemia mainly through complement-mediated cell lysis but also via direct damage to the erythrocytes membrane and phagolysis by the mononuclear phagocyte system.[4] Besides, some of *Mycoplasma*'s protein components share peptide sequence similarities with complement regulatory proteins and, therefore, they can modulate human complement activation.[5]

The first-line treatment can be either macrolides or tetracyclines; we choose tetracyclines for the patient's history of adverse effects developed with azithromycin. In our case, the response to antibiotic therapy was complete and other therapies for non-respiratory tract disease manifestations of CAD, as immunosuppressive agents, immunomodulatory therapies, or plasmapheresis, were not necessary.

Conclusions

We showed a case of ILD due to *M. pneumoniae* infection complicated by articular involvement and immune hemolytic anemia due to CAD. Primarily when the imaging findings are associated with other extrapulmonary conditions, *M. pneumoniae* should be taken into differential diagnosis in patients suspected of COVID-19. In our case, secondary autoimmune hemolytic anemia was the trigger for correct diagnosis.

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