

CASE REPORT

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Incidental late diagnosis of cystic fibrosis following AH1N1 influenza virus pneumonia: a case report

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Abstract

Background: Cystic fibrosis is an autosomal recessive disorder characterized by chronic progressive multisystem involvement. AH1N1 virus infections caused classic influenza symptoms in the majority of cystic fibrosis patients while others experienced severe outcomes.

Case presentation: We report a case of late incidental cystic fibrosis diagnosis in a young Caucasian man suffering from respiratory failure following infection due to AH1N1 influenza virus. The patient was admitted to our department with fever, cough, and dyspnea at rest unresponsive to antibiotics

Conclusions: Late diagnosis of cystic fibrosis is uncommon. This report highlights the importance of early cystic fibrosis diagnosis to minimize risk of occurrence of potential life-threatening complications.

Keywords: Pneumonia, Respiratory failure, Cystic fibrosis

Background

Cystic fibrosis (CF) is a chronic multisystem progressive disease that involves the respiratory tract, pancreas, intestine, sweat glands and reproductive tract. Worldwide incidence is 1:2500 live births with mutations carried by 1:26–27 individuals [1]. CF is a common autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane regulator gene (CFTR), classified in six subgroups on the basis of biomolecular mechanisms [1].

Improvement in diagnosis and therapy has resulted in early detection and prolonged life expectancy. CF is usually diagnosed at newborn screening (NBS) [2].

Late diagnosis (LD-CF) may occur and is being made more frequently. When CF is diagnosed in adults, it appears to be clinically different to pediatric presentation. Prognosis and life expectancy seems to be better when the disease is diagnosed in adulthood although the disease course is seriously affected by frequent respiratory infections and early bacterial colonization [2, 3].

The main cause of morbidity and mortality of CF adult patients is due to bronchial and lung involvement causing chronic bronchiectasis, which is responsible for more than 90% of fatal events. Chronic pulmonary bacterial colonization and recurrent infectious exacerbations dominate the clinical picture in CF.

Chronic pulmonary colonization is characterized by *Staphylococcus aureus* and *Haemophilus influenzae* in infancy with the appearance of *Pseudomonas aeruginosa* toward the end of the first decade, and during the second and third decades the development of pathogens such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia* and *Achromobacter* species [4, 5].

Viral infections determine inflammation and cell damage within the respiratory tract. Common respiratory viral infections are associated, in CF patients, with higher risk of mortality due to rapid deterioration of pulmonary function and an increased risk of bacterial co-infections [6, 7].

A/California/7/2009 (H1N1) virus has been responsible for a worldwide influenza pandemic [8, 9]. The majority of AH1N1 virus infections cause classic influenza symptoms while a number of patients with underlying

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medical conditions, including chronic lung disorders such as CF, experience severe disease also due to bacterial co-infection [10, 11].

Case presentation

In January 2014, a Caucasian 19-year-old man was admitted to the Department of Cardio-Thoracic and Respiratory Sciences at the Second University of Naples with severe respiratory failure secondary to a bilateral pneumonia.

Our patient reported 15 days of fever (with a maximum of temperature 40 °C) associated with productive cough; no improvement of symptoms with oral antibiotic therapy was achieved at home. On admission, our patient presented with a high fever of 40 °C, malaise, and dyspnea (Borg scale 2). Despite mild dyspnea, arterial blood gases (ABGs) on admission showed severe hypoxic respiratory failure with a partial pressure of arterial oxygen (PaO₂) of 49 mmHg, partial pressure of carbon dioxide (PCO₂) of 45 mmHg, and oxygen saturation (SpO₂) of 90% on fraction of inspired oxygen (FiO₂) 21%.

His family history revealed no respiratory disorders while his clinical history revealed frequent episodes of bronchitis and wheezing treated by a general practitioner with inhalers and antibiotics and never investigated by a pulmonologist.

A clinical examination exhibited diffuse rhonchi and crackles throughout both lung fields, digital clubbing, hypotonia with generalized muscular hypotrophy, and small body size for his age; his body mass index (BMI) on admission was 16.

Spirometry indicated the presence of a severe obstructive ventilatory defect.

A chest X-ray (CXR) exhibited extensive, undefined micronodular opacities and also mild reticular lines in the middle and lower thoracic fields (Fig. 1).

Blood examinations showed normochromic normocytic anemia (Hgb (haemoglobin) 10,6 g/dL), marked leukocytosis (31.18*10³u/L), and hypergammaglobulinemia (IgG (immunoglobulin G) 2136 mg/dL).

AH1N1 virus infection was laboratory confirmed on pharyngeal swab by using a real-time reverse-transcriptase polymerase chain reaction assay (rapid diagnostic test for H1N1 influenza virus (FAST SET) H1N1v Arrow Diagnostic srl Genova, Italy).

Concurrent *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex infection was detected on sputum microbial examination; antibiotic therapy was administered as follows: piperacillin-tazobactam 4.5gr intravenously three times a day and ciprofloxacin 400 mg intravenously twice a day in addition to oseltamivir orally. Our patient was placed in isolation in a

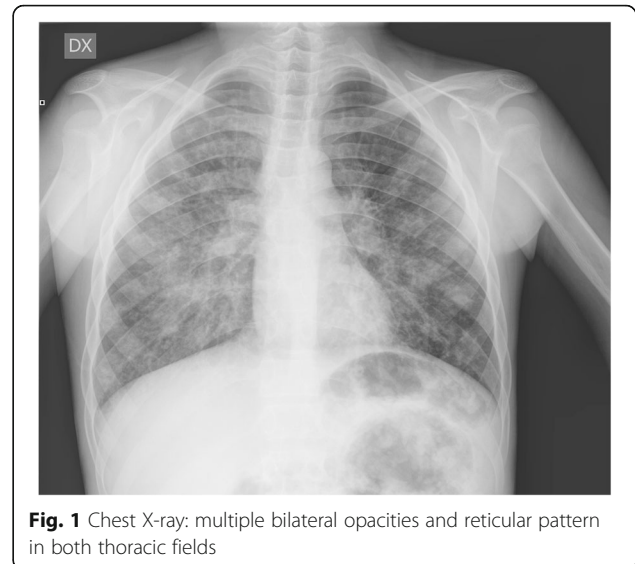


Fig. 1 Chest X-ray: multiple bilateral opacities and reticular pattern in both thoracic fields

negative pressure room until pharyngeal swabs for AH1N1 were clear.

Despite pharmacological therapy and oxygen support, his clinical state remained poor. His PO₂ value was 60 mmHg and PCO₂ 44 mmHg on oxygen via a 40% venturi mask.

A high-resolution computed tomography (HRCT) scan identified multiple cylindrical bronchiectasis and bronchiolectasis in both lungs as well as mucous plugging and centrilobular nodules. Also evident in some areas were “tree-in-bud opacities”, an expression of acute small airways disease. An incidental finding was adipose infiltration of the pancreas (Fig. 2).

At this stage clinical and radiological findings raised suspicion of CF; therefore, our patient underwent a sweat test, which exhibited clear positive values (a Na⁺ of 103 mEq/L and Cl⁻ 94 mEq/L) and a molecular test

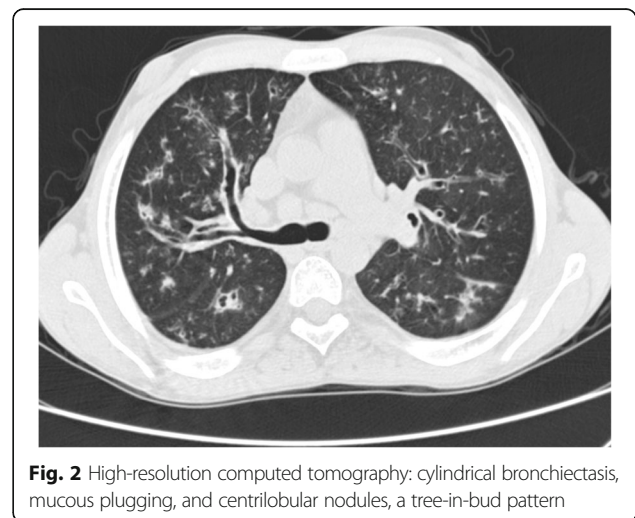


Fig. 2 High-resolution computed tomography: cylindrical bronchiectasis, mucous plugging, and centrilobular nodules, a tree-in-bud pattern

with deoxyribonucleic acid (DNA) extraction and analysis of CFTR gene mutations confirming disease (genotype DeltaF508/DeltaF508).

Our patient was then transferred to the Adult Cystic Fibrosis Department of Federico II Hospital, University of Naples; a clinical examination showed the presence of dyspnea (Borg scale 3), fever (a temperature of 39 °C), asthenia, cachectic appearance, immobilization syndrome, presence of diffuse rhonchi, and crackles throughout both lung fields as well as a sacral pressure sore (stage 1).

ABGs on oxygen therapy with a nasal cannula (4 L/min) showed values of PCO₂ of 34.4 mmHg and PO₂ of 58.1 mmHg.

Blood examinations confirmed anemia (hemoglobin 8.8 g/dL), marked leukocytosis 20,000/L, hypergammaglobulinemia and C-reactive protein (PCR) of 5.14 mg/dL; persistence of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex was showed on sputum. Parenteral antibiotic therapy was continued as follows: meropenem 2 g intravenously three times a day, ceftazidime 3 g intravenously three times a day, colistin 2,000,000 intravenously three times a day. Further therapy included acetylcysteine intravenously, twice a day, electrolytic 0.9% solution, intravenously, betamethasone 1.5 mg, intravenously, twice a day.

A program of drainage physiotherapy was started using ELTGOL (slow expiration with glottis opened in lateral posture, French: Expiration Lente Totale Glotte Ouverte en décubitus Latéral), positive expiratory pressure (PEP) mask, Acapella and autogenous drainage twice a day. To improve his bronchial hygiene and physiotherapy, nebulized hypertonic saline 3% solution was administered.

An air mattress was used to aid healing of a sacral pressure sore and low molecular weight heparin was administered while our patient was immobile. Parenteral ferrous sulfate was prescribed to treat anemia. Dietary assessments were carried out during admission to optimize nutritional intake.

His pancreatic insufficiency was treated with pancreolipase and the diabetes was well controlled with rapid-acting insulin three times daily and long-acting insulin therapy overnight.

During the 3 months' admission, our patient demonstrated significant improvement in his respiratory symptoms; normalization of arterial blood gas values, good glycemic control, satisfactory weight gain (BMI 18), resolution of his sacral pressure sore, and improvement in his energy levels leading to remobilization [12].

Our patient was discharged to attend rehabilitative therapy as an outpatient (Table 1).

Discussion

Although CF is usually discovered early in life, it is no longer only a pediatric disease.

Table 1 Clinical and functional data of our patient at 1-year follow-up

	T0	T1	T3	T6	T12
FEV ₁	29%	30%	38%	40%	40%
BMI	16	16	18	19	19
SpO ₂	90%	90%	93%	95%	95%
Number of bronchial exacerbation	/	0	0	1	1

T0 time of admission, T1 1 month later diagnosis, T3 3 month later diagnosis, T6 6 month later diagnosis, T12 12 month later diagnosis, FEV₁ forced expiratory volume in the 1st second, BMI body mass index, SPO₂ peripheral capillary oxygen saturation

As is reported in the literature, patients who receive early diagnosis of CF suffer from a combination of gastrointestinal and pulmonary symptoms, while respiratory disorders are more common when diagnosis is late. In adulthood, CF may be diagnosed on the basis of isolated symptoms ranging from male infertility to episodes of recurrent pancreatitis [3]; other patients have mild symptoms mimicking other respiratory disorders [13, 14] with absence of digestive symptoms.

In our case, despite extensive lung involvement, late diagnosis of CF was incidentally performed following severe respiratory infection due to AH1N1 influenza virus. Advances in diagnostic procedures, including imaging [15, 16], have contributed to early cystic fibrosis suspicion on admission. Late diagnosis (LD-CF) is possible and is defined as an individual who fulfils the criteria for CF and is either NBS-negative (LD-NBS-neg) with a negative immunoreactive trypsinogen (IRT) or genotype, or NBS-positive but with a sweat chloride (SC) < 60 mmol/L [3, 17].

The sweat test of Gibson and Cooke remains the most sensitive and cheapest method for CF diagnosis when carried out in high specialization centers. In Italy, CF diagnosis is performed using a neonatal screening procedure; this minimizes the occurrence of late diagnosis.

Chronic respiratory disorders arising from different pathways [18–21] have been linked to severe lung involvement leading to respiratory deterioration, requiring oxygen support or mechanical ventilation and even death in AH1N1 virus infection.

Viral infections seems to have the same occurrence between CF and healthy subjects but patients suffering from CF are more frequently symptomatic and the course of the disease worse. The role of pandemic A (H1N1) virus infection in CF patients is unclear, but these patients seem to be more susceptible to the infection. Severe respiratory involvement is an important risk factor for intensive care unit (ICU) admission and death [22–24].

Conclusions

The widespread availability of centers for the analysis of CFTR and the discovery of new drugs modulating the

chloride protein channel have resulted in a raised awareness of cystic fibrosis diagnosis [1, 17] in adult patients also.

The diagnosis should be considered even when non-typical symptoms are exhibited. Missed CF diagnosis and treatment has been responsible, in our case, for a severe and potential life-threatening respiratory complication caused by AH1N1 influenza virus infection.

It is important to reduce the occurrence of late CF diagnosis and promote appropriate patient care.

Abbreviations

ABG: Arterial blood gases; CF: Cystic fibrosis; CFTR: Cystic fibrosis transmembrane regulator gene; CXR: Chest X ray; HRCT: High-resolution computed tomography; LD-CF: Late-diagnosis cystic fibrosis; LD-NBS-neg: Late diagnosis – negative newborn screening

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Availability of data and materials

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Authors' contributions

CI wrote the manuscript and managed the patient. AB wrote the manuscript and managed the patient. CC carried out the initial management of the patient. GM reviewed the manuscript. GR performed imaging evaluation. PI helped in the management and follow-up of the patient. VC helped in the management and follow-up of the patient. NF reviewed the manuscript. FP reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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