DOI: 103126/JNPS.V4113

Case Report

Progressive Pulmonary Disease in X-Linked Agammaglobulinemia despite Regular Immunoglobulin Replacement: A Case Report

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Article History

Received on - 2024 Dec 16
Accepted on - 2025 Jan 24

Keywords:

Immunoglobulin replacement; Progressive pulmonary disease; X-linked agammaglobulinemia

Online Access

DOI: https://doi.org/10.60086/jnps1266

Abstract

X-linked agammaglobulinemia (XLA) is characterized by early-onset recurrent bacterial infections, particularly affecting the respiratory tract. We report a 12 year old male with XLA who presented with chronic cough and recurrent respiratory infections. Genetic testing confirmed a BTK (Bruton tyrosine kinase) gene mutation. Radiological findings revealed diffuse cylindrical bronchiectasis with bilateral bronchial wall thickening, and pulmonary function tests showed a mixed severe ventilatory pattern. Despite regular immunoglobulin replacement therapy, the patient developed chronic lung disease, highlighting the need for early diagnosis and aggressive management of respiratory manifestations.

Introduction

X-linked agammaglobulinemia (XLA) is a prototype of primary humoral immunodeficiency, first described in 1952. It is caused by pathogenic variants in the Bruton tyrosine kinase (BTK) gene, leading to absent or very low numbers of circulating B lymphocytes, low levels of serum immunoglobulins, and severely impaired antibody production. The disease prevalence is estimated between 1 / 100,000 and 1 / 200,000.[1] Respiratory tract represents the most affected organ system, documented in 51.2% of patients, followed by gastrointestinal (40%) and neurological manifestations (35.4%).[1] Recent studies have shown that respiratory tract complications occur in up to 85.2% of patients, with pneumonia being the most frequent presentation (62.6%).[2] Despite regular immunoglobulin replacement therapy (IRT), patients continue to experience complications that impact organ function, with the cumulative risk for chronic lung disease reaching 47% after 40 years of follow-up.[3] Distinct patterns of pulmonary involvement can be identified through imaging, ranging from bronchiectasis to alveolar opacification.[4] These changes can occur even in patients with adequate IRT, suggesting that additional factors beyond antibody deficiency contribute to lung damage.[5,6]

Case Report

A 12-year-old male patient with a previous diagnosis of XLA was admitted for chronic cough. He was born to non-consanguineous parents and had seven healthy sisters, with no similar cases in the family. The diagnosis of XLA had been established based on recurrent infections including pneumonia, chronic mucoid diarrhea, and bilateral knee septic arthritis due to Haemophilus influenzae. Immunological workup showed markedly decreased immunoglobulin levels and CD19 count at 0%. Further testing revealed absence of vaccine responses and bone marrow immunophenotyping demonstrated a maturation block at the pre-B cell stage.

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Genetic testing was performed and confirmed the presence of a BTK gene mutation.

The patient was diagnosed with XLA at age three years, after a two year history of recurrent infections. Initial treatment consisted of monthly intravenous immunoglobulin (IVIG) infusions at 400 mg / kg and prophylactic antibiotics (co-trimoxazole). He also received fluticasone and salbutamol for respiratory symptoms. Although treatment compliance was good, with adequate IgG trough levels (> 7 g / L) and a significant reduction in infection frequency, IVIG treatment was discontinued this past month due to supply issues. This treatment gap led to the current episode, which evolved over one month, characterized by dry cough without fever. There were no signs of tuberculosis infection and his general condition remained preserved, likely due to the protective effect of his previous consistent IRT. Physical examination revealed a normal boy with digital clubbing, bilateral rhonchi, and thoracic deformity. Laboratory investigations showed normal CBC, elevated CRP, and severely decreased immunoglobulins (IgG < 3.2 g / L, IgA < 0.25 g / L, IgM < 0.25 g / L). Sputum cultures were negative for Pseudomonas and QuantiFERON test was negative. Imaging studies demonstrated significant pulmonary involvement. The chest X-ray showed bilateral reticular opacities with prominent bronchial wall thickening, particularly marked in the lower zones (Figure 1).

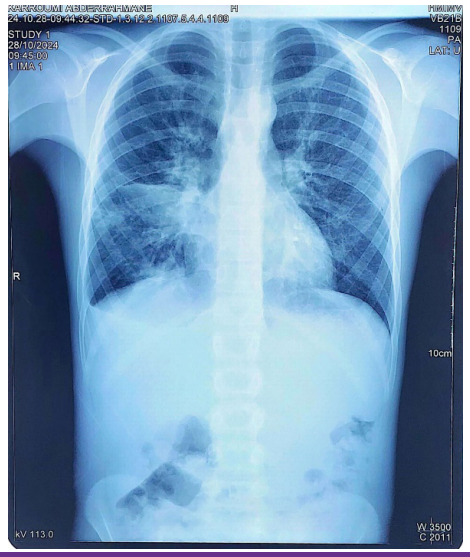


Figure 1. Chest X-ray showing bilateral reticular opacities and bronchial wall thickening

These findings were further characterized by chest CT scan, which revealed diffuse cylindrical bronchiectasis with bronchial wall thickening predominantly affecting the lower lobes, a pattern characteristic of chronic lung disease in XLA patients (Figure 2).

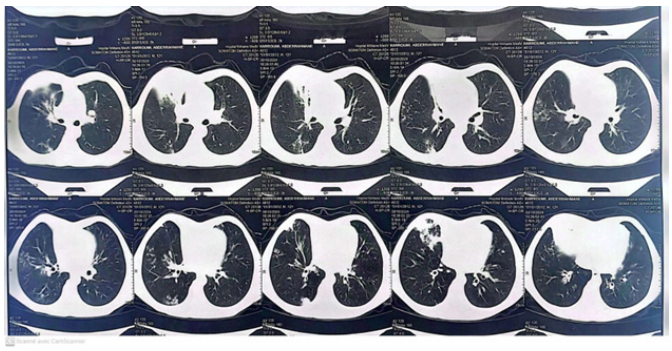
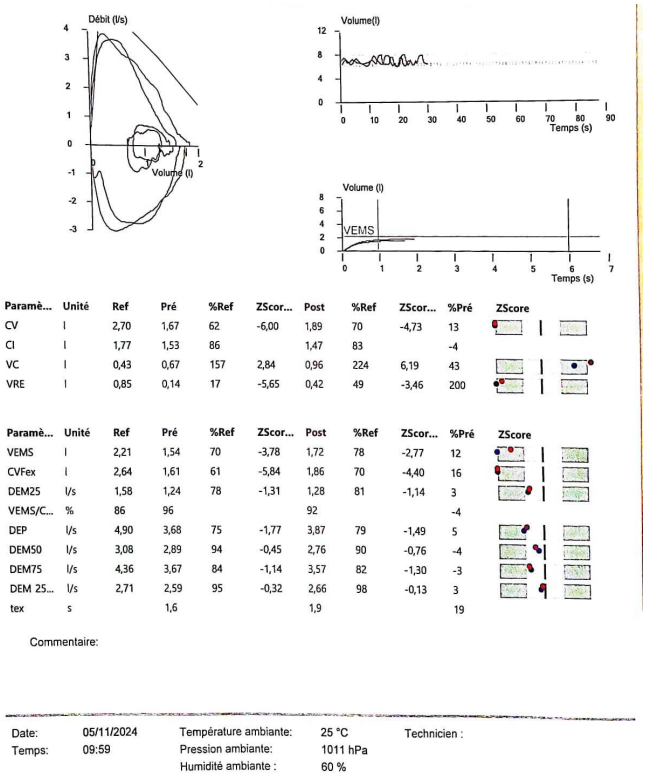


Figure 2. Chest CT scan showing diffuse cylindrical bronchiectasis with bronchial wall thickening

Pulmonary function testing demonstrated a mixed severe ventilatory pattern combining both restrictive and obstructive components. The patient showed significant bronchodilator reversibility with marked improvement in flow rates following salbutamol administration (Figure 3).



Paramè...	Unité	Ref	Pré	%Ref	ZScor...	Post	%Ref	ZScor...	%Pré	ZScore
CV	l	2,70	1,67	62	-6,00	1,89	70	-4,73	13	
CI	l	1,77	1,53	86		1,47	83		-4	
VC	l	0,43	0,67	157	2,84	0,96	224	6,19	43	
VRE	l	0,85	0,14	17	-5,65	0,42	49	-3,46	200	

Paramè...	Unité	Ref	Pré	%Ref	ZScor...	Post	%Ref	ZScor...	%Pré	ZScore
VEMS	l	2,21	1,54	70	-3,78	1,72	78	-2,77	12	
CVFex	l	2,64	1,61	61	-5,84	1,86	70	-4,40	16	
DEM25	l/s	1,58	1,24	78	-1,31	1,28	81	-1,14	3	
VEMS/C...	%	86	96			92			-4	
DEP	l/s	4,90	3,68	75	-1,77	3,87	79	-1,49	5	
DEM50	l/s	3,08	2,89	94	-0,45	2,76	90	-0,76	-4	
DEM75	l/s	4,36	3,67	84	-1,14	3,57	82	-1,30	-3	
DEM 25...	l/s	2,71	2,59	95	-0,32	2,66	98	-0,13	3	
tex	s		1,6			1,9			19	

Commentaire:

Date: 05/11/2024 Température ambiante: 25 °C Technicien :
Temps: 09:59 Pression ambiante: 1011 hPa
Humidité ambiante : 60 %

Figure 3. Pulmonary function test results showing a mixed ventilatory pattern with positive bronchodilator response

Discussion

Our case illustrates the complex nature of pulmonary involvement in XLA, which remains a major challenge even with appropriate IRT. Current guidelines recommend initial IVIG dosing at 400 - 600 mg / kg every 3 - 4 weeks, with a target trough IgG level > 5 g / L. In our patient, the initial loading dose was 1 g / kg over 48 hours, followed by monthly maintenance infusions of 1 g / kg, which exceeds the minimum recommended dose. Monitoring showed sustained trough IgG levels > 7 g / L, and this aggressive replacement strategy resulted in a significant reduction in infectious episodes. Additionally, prophylactic antibiotics (co-trimoxazole) were appropriately prescribed as recommended for patients with recurrent respiratory infections. This approach aligns with current best practices that emphasize the importance of maintaining adequate immunoglobulin levels and preventing infections to minimize long-term pulmonary complications. Regular monitoring of trough levels and clinical response allows for dose adjustments as needed to optimize outcomes. The progression of respiratory disease in this patient follows the typical pattern described in recent literature, with several important aspects worth discussing. The radiological manifestations observed in our patient, particularly the cylindrical bronchiectasis predominantly affecting the lower lobes, represent the most common pattern of chronic lung disease in XLA. According to Bondioni et al, cylindrical bronchiectasis is found in 61.5% of cases, with a characteristic lower lobe predominance.[7] This pattern of bronchiectasis develops through a complex pathogenic process, where recurrent infections, chronic inflammation, and possibly aberrant tissue repair mechanisms contribute to progressive airway damage. The bilateral distribution and the extent of bronchiectasis in our patient, despite his young age, underscore the aggressive nature of pulmonary involvement in XLA.

The pulmonary function abnormalities observed in our case reflect the heterogeneous nature of respiratory involvement in XLA. The mixed ventilatory pattern we observed, combining both restrictive and obstructive components, is consistent with recent findings by Fekrvand et al, who reported mixed patterns in 36.8% of cases.[2] This functional profile likely results from multiple pathogenic mechanisms: bronchiectasis and airway inflammation leading to obstruction, while chronic inflammation and subsequent fibrosis contribute to restriction. The positive bronchodilator response in our patient suggests ongoing airway reactivity, which may represent a therapeutic target beyond IRT.

The progression of pulmonary disease despite adequate IRT raises important questions about disease pathogenesis. Recent studies suggest inadequate tissue penetration of replacement immunoglobulins, particularly at the bronchial mucosa level, may leave these areas vulnerable to infection and inflammation.[4] The early onset of infections, often preceding diagnosis, may establish a cycle of inflammation and tissue damage that continues despite subsequent adequate treatment.[3] Additionally, the absence of B-cells may have consequences beyond antibody deficiency, possibly affecting local immune responses and tissue repair mechanisms.[5] The cumulative risk of chronic lung disease reaching 47% after 40 years of follow-up, even with optimal treatment, suggests that current therapeutic approaches may be insufficient.[3]

This observation has driven increasing interest in complementary therapeutic strategies. Our experience with this case, supported by recent literature, suggests that management of pulmonary disease in XLA requires a comprehensive approach combining early initiation of IRT at optimal doses, systematic pulmonary surveillance including regular imaging and pulmonary function testing, and aggressive management of acute infections. The implementation of airway clearance techniques and bronchodilators, along with consideration of anti-inflammatory treatments in selected cases, may also play crucial roles in management. These observations support the need for prospective studies to evaluate more aggressive therapeutic approaches and to identify biomarkers that might predict disease progression.

Conclusions

This case underscores the crucial importance of early diagnosis and close monitoring of respiratory manifestations in XLA. Despite adequate IRT and other complementary treatments, there may be progression of lung disease.

Conflict of Interest: None

Funding Source: None

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