A rare genetic cause of bronchiectasis

O cauză genetică rară de bronșiectazii

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Abstract

Bronchiectasis, defined as an abnormal and irreversible dilatation of the bronchi, frequently associated with inflammation, is the most common complication of recurrent infections. Effective pulmonary immunity is necessary to prevent chronic bronchial damage due to bacterial infection. Primary immune deficiencies comprise a heterogeneous group of genetically determined disorders that affect development and/or the function of innate or adaptive immunity. In multiple series reported in literature, common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) and chronic granulomatous disease (CGD) were the most common forms of primary immune deficiencies (PIDs) associated with bronchiectasis[1,15]. Despite advances in the molecular knowledge of PIDs during the past two decades, there are many undiagnosed or late diagnosed patients[6,14]. We report a case of Bruton's disease late diagnosed, already with bronchiectasis, with an early onset of recurrent respiratory infections.

Keywords: ***X-linked agammaglobulinemia, Bruton's disease, primary immunodeficiency, bronchiectasis***

Rezumat

Bronșiectaziile, definite ca o dilatare anormală și ireversibilă a bronhiilor, frecvent asociate inflamației, sunt cea mai frecventă complicație a infecțiilor recurente. O imunitate pulmonară eficientă este necesară pentru a preveni deteriorarea bronșică cronică cauzată de infecții bacteriene. Imunodeficiențele primare (IDP) cuprind un grup heterogen de tulburări determinate genetic care afectează dezvoltarea și/sau funcția de imunitate înnăscută sau dobândită. În mai multe studii raportate în literatura de specialitate, imunodeficiența comună variabilă, agamaglobulinemia X-linkată și boala granulomatoasă cronică au fost raportate ca fiind cele mai frecvente forme de IDP asociate bronșiectaziilor[1,15]. În pofida progreselor și a competențelor până la nivel molecular, obținute pe parcursul ultimelor două decenii în domeniul IDP, mai există un număr mare de cazuri nediagnosticate sau tardiv diagnosticate[6,14]. Prezentăm un caz de boală Bruton diagnosticat tardiv, după apariția bronșiectaziilor, ce prezenta infecții respiratorii recurente debutate la vârsta de sugar.

Cuvinte-cheie: ***agamaglobulinemia X-linkată, boala Bruton, imunodeficiență primară, bronșiectazii***

Introduction

Bronchiectasis, defined as an abnormal and irreversible dilatation of the bronchi, is frequently associated with inflammation within the bronchial wall as a result of an infection within the airway, inhalation of injurious agents or an endogenous condition such as an autoimmune disease, all modulated by immune response. As a consequence, inherited or acquired immunodeficiencies can drive the development and progression of bronchiectasis.

Case report

A 19-year-old male was admitted to our clinic for cough, purulent expectorations (80 ml daily), hemoptysis, important dyspnea (MRC 3), fever up to 40°C, chills, loss of appetite and marked asthenia.

Physical examination revealed a BMI of 21 (measuring 180 cm and weighting 68 kg), the patient presented on the upper and lower limbs multiple areas of hyperpigmentation after pyodermas (Figure 1A). There were no palpable lymph nodes, and tonsillar tissue was hypoplasic with mild hyperaemia of the oropharyngeal isthmus (Figure 1C). Consolidation syndrome was found in the lower left lobe. Respiratory rate was 26/minute and oxygen saturation (SaO_2) was 92% in ambient air. The liver and the spleen were normal.

The chest radiography showed bilateral pneumonia with pleural effusion, which improved after seventeen days of antibiotic treatment, but the appearance of a smooth interstitial involvement in the right lower field was observed (Figure 2 A, B). After two days, new lung opacities in the right lung were clearly demonstrated (Figure 2 C) associated with general signs of inflammatory response (fever, shivers and pleuritic chest pain). The sputum cultures identified *Streptococcus pneumoniae* sensitive to doxicycline, cefuroxime, ceftriaxone, ofloxacine, ciprofloxacine and resistant to amoxixilline-clavulanate, gentamycine, eritromycine, and lincomycine. A cardiac ultrasound excluded congenital heart diseases and endocarditis.

The history of recurrent pneumonias in different lobes (three episodes earlier in 2014 – Figure 3) raised the suspicion of bronchiectasis and cystic fibrosis. Sweat test was negative, but cylindrical bronchiectasis (Figure 4) was confirmed in 2015 by chest high resolution tomography (more extensive in the left lower lobe, the most frequent site of the previous pneumonias according the radiological archive). An immune suppression as a risk factor for pulmonary infections was suspected. HIV tests were negative.

A more detailed medical history revealed that from the age of 2 months the patient was observed with ite-

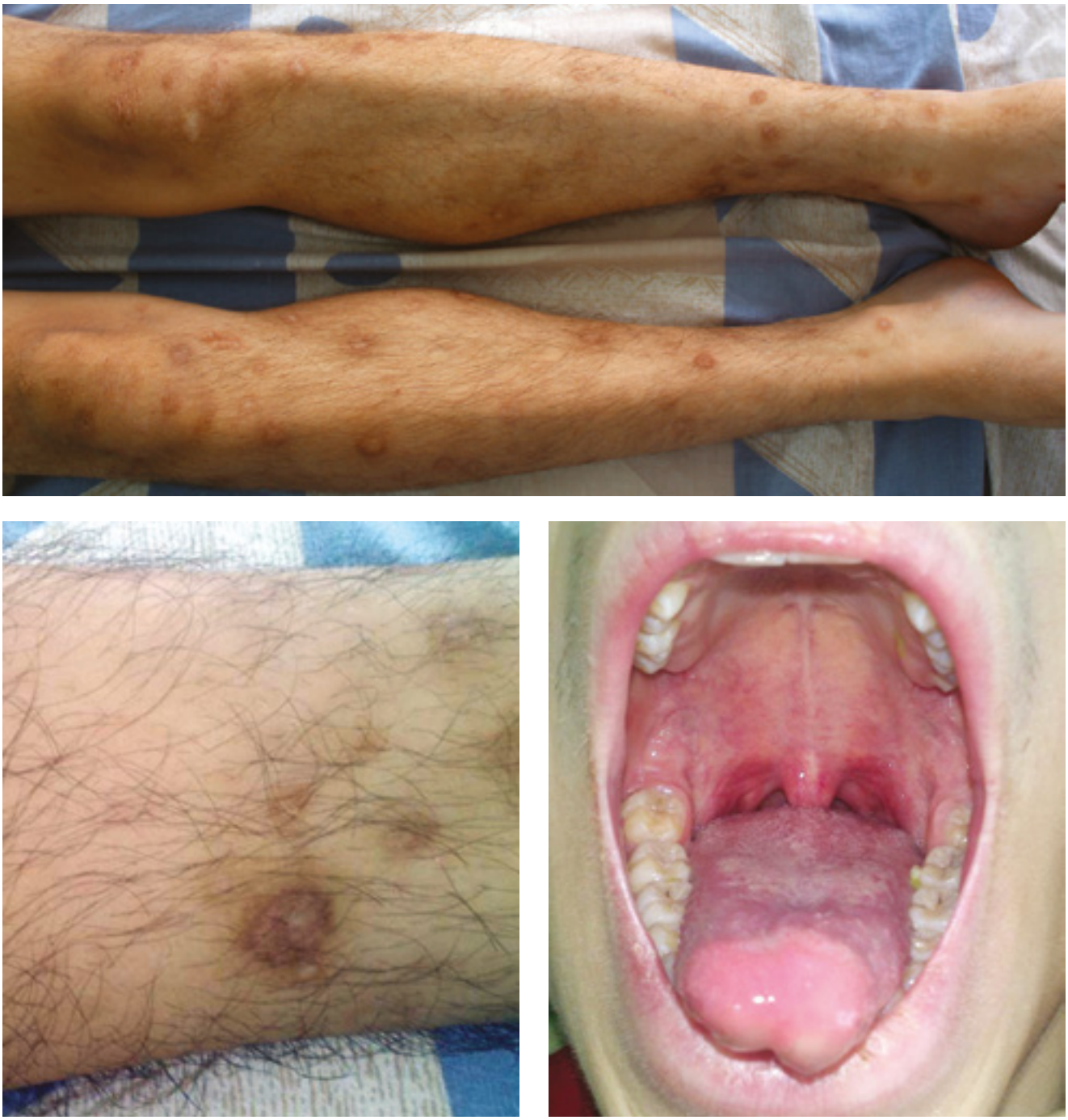
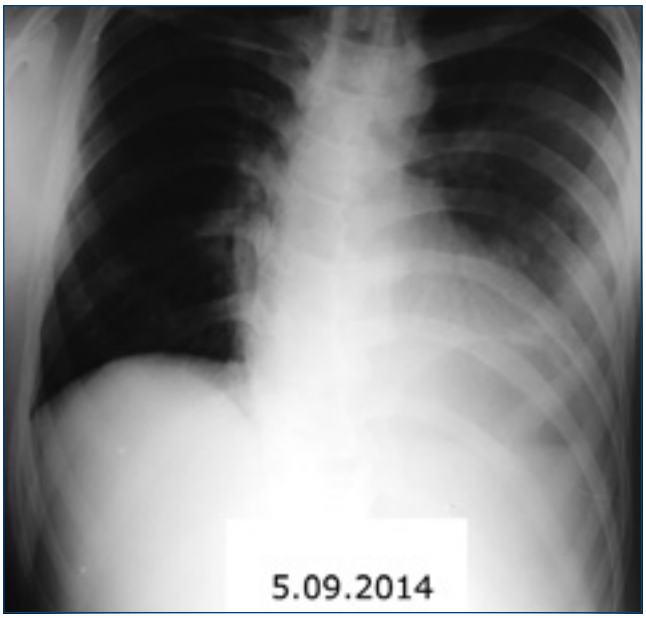


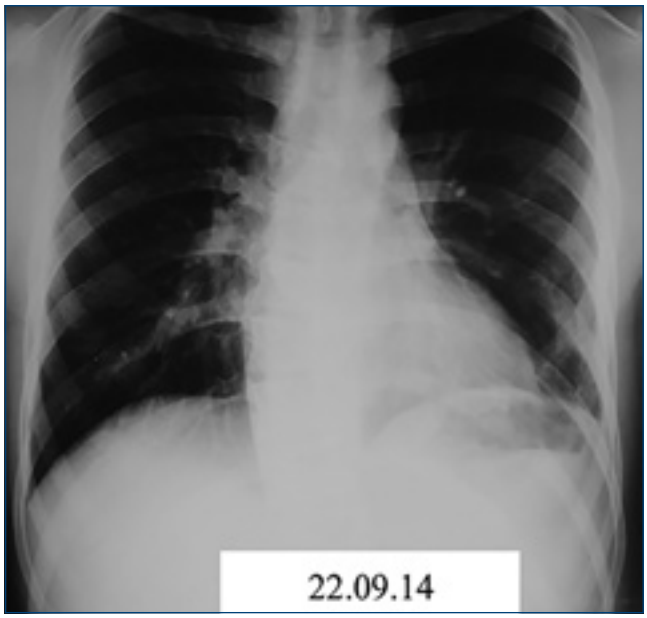
Figure 1. *A, B - postinflammatory hyperpigmentation after insect bites manifested as darkly-pigmented macules on the legs. C - hypoplastic tonsillar tissue and mild hyperaemia of the oropharyngeal isthmus*

rative infections (more than 10 episodes per year): nasopharyngitis, conjunctivitis, otitis, purulent sinusitis, bronchitis, pneumonia (the first at the age of 6 month). Right sided pyothorax as a complication of pneumonia was reported at the age of 13. A four-year period without symptoms (from 14 to 18 years) was followed by a widespread pyoderma on the legs after insect bites. There are no available data about the immunoglobulin level at that time. The antibacterial treatment (using penicillins, macrolides, cephalosporins, sulfonamides and aminoglycosides in different combinations) was effective in all infectious episodes.

The only child of non-consanguineous parents, born eutrophic, breastfed for 10 months, the patient received all the vaccines included in the national schedule but with some delays because he had been suffering from frequent infections from an early age. There was no family history of immunodeficiency (his two cousins are healthy).

Because antibodies and phagocytes are the primary defense against recurrent bacterial infections, measurement of serum immunoglobulins and analysis of neutrophil count and function were considered (searching for an underlying immune defect in patients with chronic lung disease).





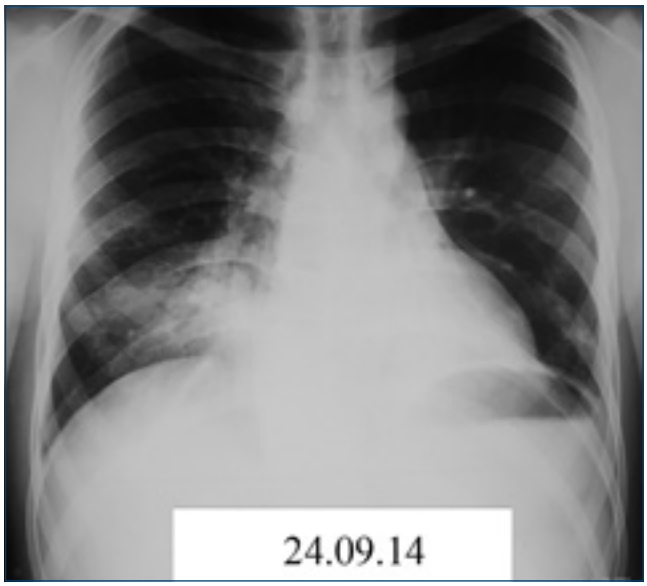


Figure 2. A – *posteroanterior chest X-ray shows extensive opacification of nearly entire left lung that gradually diminishes upward with Felson sign and aeric bronchograms. On the right hemidiaphragm, elevation due to subpulmonic pleural effusion and a consolidation syndrome in the perihilar area. The right lateral cardiac margin is indistinct (silhouette sign)*

B – *the radiograph after 17 days of antibiotic therapy demonstrates a resolution of the opacities on the left side and of the pleural effusion on the right. Some linear opacities remain in both lower fields, caused by diffuse bronchial wall thickening and bronchiectasis confirmed on HRCT one year before (Figure 4).*

C – *after two days, new infiltrations appear in the right lower lobe considered as a manifestation of nosocomial pneumonia*

Hypogammaglobulinemia was identified by serum protein electrophoresis: albumin - 61.1%, α_1-globulin - 7.2%, α_2 - 18%, β_1 - 7.7%, β_2 - 4.9%, γ - 1.1% (normal: 6.2-15.4%) – Figure 5.

Two methods were used for the identification of the immunoglobulin levels. The radial immunodiffusion method of Mancini detected the following changes: IgA - 0 (normal range: 1.25-3.95 g/l), IgG - 0 (normal range: 8.45-16.1 g/l) and IgM - 0.4 g/l (normal range: 0.58-2.22 g/l). The turbidimetric method identified: IgA - 30 mg/dl (normal range: 70-400 mg/dl), IgG - 53 mg/dl (normal range: 700-1600 mg/dl), and IgM - 9 mg/dl (normal range: 40-230 mg/dl).

The immunophenotyping of lymphocytes subpopulation using monoclonal antibodies revealed a severe central humoral immunodeficiency (significantly reduced B cells - 0.25%): total lymphocytes - 2400/mm^3, CD3 - 94% (normal: 65-79%), CD4 - 41% (normal: 33-44%), CD8 - 39% (normal: 19-27%), CD16 - 6% (normal: 6-18%), CD20 - 0.25% (normal: 3-15%), CD4/CD8 - 1.05 (normal: 1.6-2.1), CD4+CD8/CD3 - 0.85 (normal: 0.86-1.1).

Genetic analysis revealed a mutation resulted regulatory defect IVS1+5G>A hemizygous nucleotide change in intron 1 of BTK gene (Department of Infectious Diseases and Pediatric Immunology, University of Debrecen, Hungary). The patient's mother was found to carry the same mutation.

Discussion

Primary immune deficiencies (PIDs) consist of a heterogeneous group of over 250 inherited disorders, characterized by different defects in the development and function of the immune system. They are among the causes for secondary bronchiectasis[1,15].

According to the ESID (European Society for Immunodeficiencies) Registry, the prevalence of PIDs documented in 2011 in Eastern Europe ranges from 0 to 2.5 patients per 100,000 population and is much lower

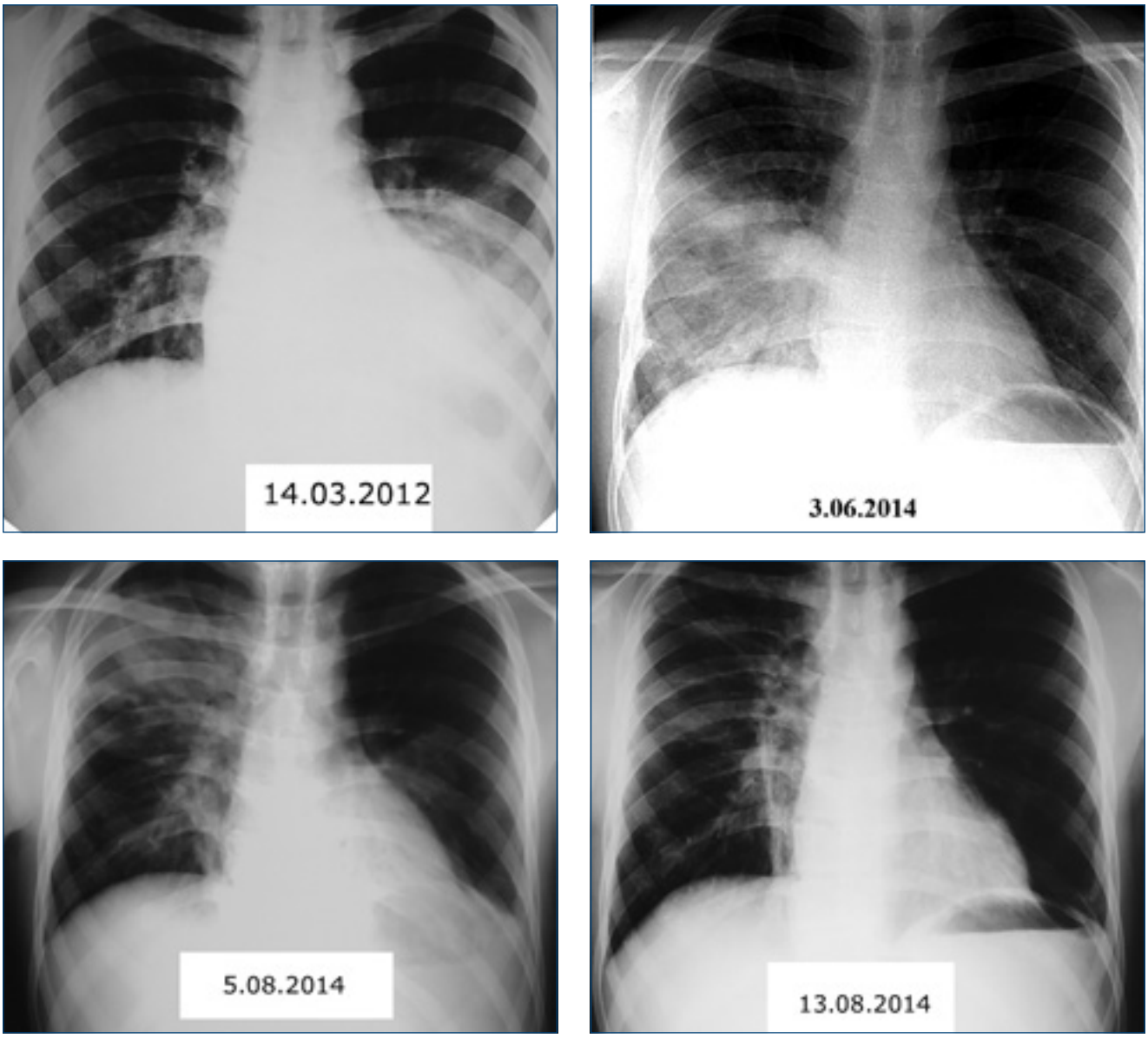


Figure 3. *Chest radiographs confirming recurrent pneumonias with variable lobar distribution in the previous years*

than in France (5.13) and Spain (4.13)[2,9]. XLA prevalence in the USA[3] is 1 patient in 250,000 population and in Central and Eastern Europe - 1 in 400,000[4].

In the Republic of Moldova, there are no statistical data on the prevalence of PIDs. According to a local 10-year morphological study among 2348 cases of infant death (1990-2000), 37 cases with primary immunodeficiency were detected, representing 1.6% of total deaths[5].

The most common category of these disorders associated with bronchiectasis is the group of antibody deficiencies. The selective IgA deficiency, or transient hypogammaglobulinemia of infancy, is an immunodeficiency with a quite high prevalence. It is usually asymptomatic or with mild clinical manifestation. X-linked agammaglobulinemia and hyper-IgE syndrome represent another group of humoral immunodeficiencies with low prevalence but with more severe clinical evolution. The most common clinical presentation of this humoral PIDs group is recurrent infections (especially encapsulated bacteria, enteroviruses, *Giardia lamblia*).

X-linked agammaglobulinemia (XLA), also named Bruton's disease (inherited humoral immunodeficiency caused by mutation in the Bruton's tyrosine kinase gene), was first described by Ogden Bruton in 1952 and the gene whose mutation causes XLA was discovered in 1993.

The classification of primary immunodeficiencies is reviewed by the Expert Committee of the International Union of Immunological Societies every 2-3 years. According to the classification of PIDs updated in 2014, X-linked agammaglobulinemia is a deficiency that affects predominantly antibody production, causing the severe reduction of all classes of immunoglobulins and low level or absence of B lymphocytes[8].

The genetic disorder is caused by an arrest in the differentiation of the B-cell precursors in the bone marrow. The gene that is mutated in XLA has been localized at the long arm of chromosome X (Xq21.3-q22) and has been termed Bruton's tyrosine kinase (BTK) as it has been

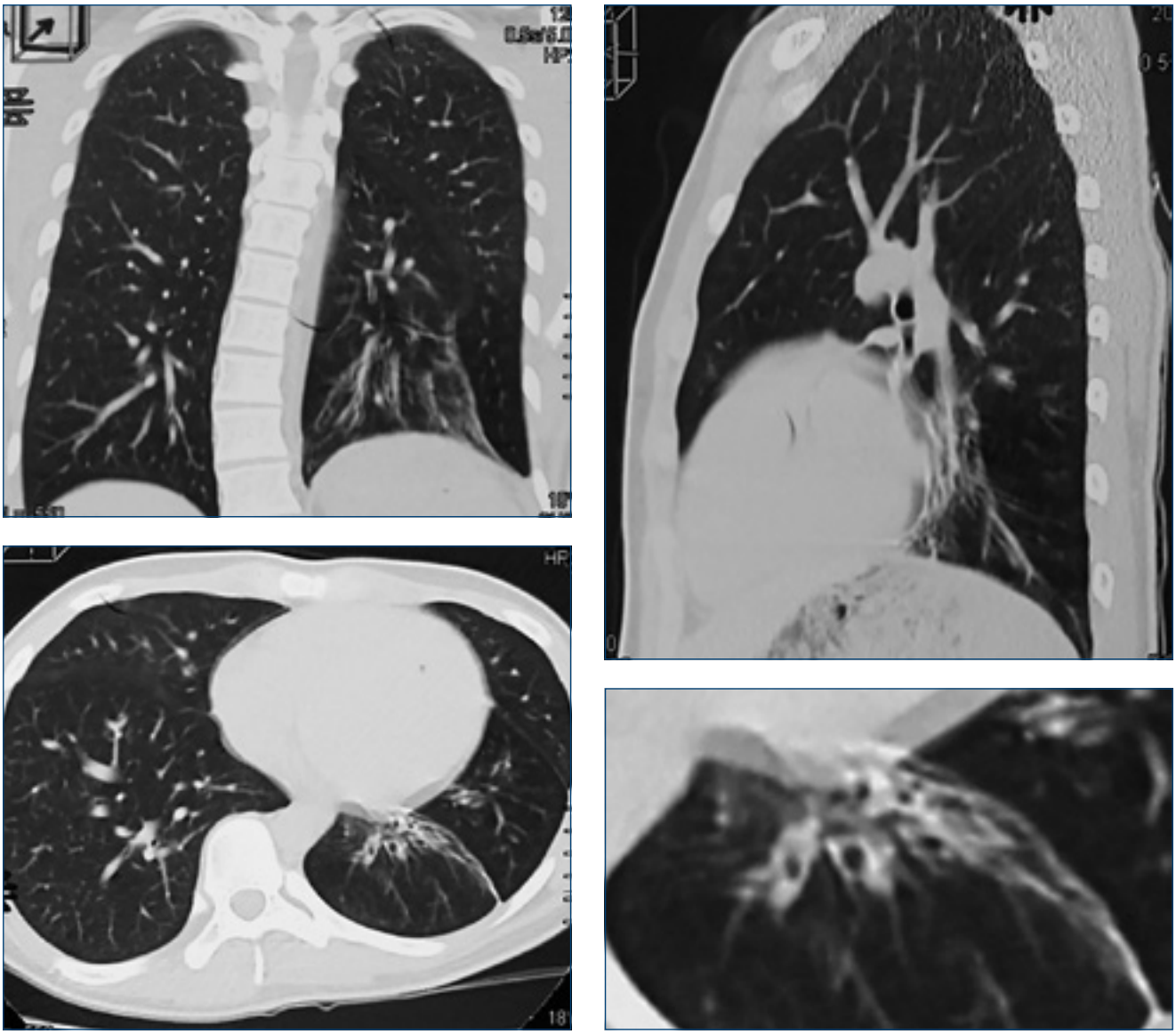


Figure 4. *High-resolution computed tomography images show lower lobes bronchiectasis (thickened bronchial walls, "signet ring" sign, tram-tracks sign) and volume loss*

shown to encode a cytoplasmic tyrosine kinase. The gene consists of 19 exons spread over 37.5 kb of DNA. The protein product (BTK - composed of 659 amino acids) is a critical component of multiple B-cell signaling pathways, which are essential for B lymphocyte proliferation, differentiation and survival. The absence of mature B cells leads to the hypoplasia of all the lymphoid tissue (tonsils, adenoids, peripheral lymph nodes, MALT).

XLA is a disorder that affects only males, while girls are only carriers and have no clinical manifestations. The first signs of the disease normally appear after 6 months of age, when maternally derived IgG disappear. Affected males develop recurrent infections of different organ systems, mainly upper and lower respiratory tract (90%) and gastrointestinal infections, but also bacterial skin infections, meningitis or sepsis[10].

The bronchiectasis occurs earlier in X-linked agammaglobulinemia compared to common variable immune deficiency (CVID), probably due to the precocious onset of pulmonary infections in the first one. It seems that the majority of the hypogammaglobulinemic patients suffer from the mild type of bronchiectasis. Regarding the clinical characteristics of bronchiectasis, they are in general bilateral and diffuse, most commonly found in the middle or lower lobes. In the majority of the cases, tubular (cylindrical) bronchiectasis are observed, whereas varicose and cystic types are less common[1,7,15].

The European Society for Immunodeficiencies Registry defined the criteria for a probable XLA diagnosis (clinical diagnosis): fewer than 2% circulating B cells (CD19 and CD20), preferably in two separate determinations **AND** a normal number of T cells (CD3, CD4 and CD8) **AND** serum IgG levels below 200 mg/dl in infants aged <12 months, below 500 mg/dl in children aged >12 months **OR** normal IgG levels with IgA and IgM below 2x standard deviation **AND** onset of recurrent infections before 5 years of age **OR** positive maternal family

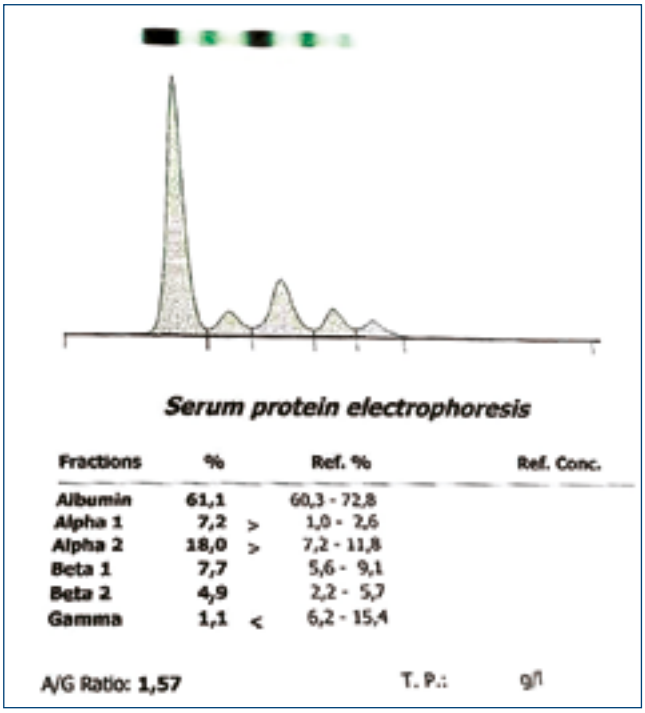


Figure 5. *Abnormal serum protein electrophoresis pattern with hypogammaglobulinemia*

history of agammaglobulinemia[9].

Clinical phenotype of our patient has evolved from frequent acute to chronic respiratory infections which required iterative hospital admissions. He also developed repeated ENT (ear, nose, throat) infections (bilateral otitis and sinusitis), bacterial conjunctivitis and pyoderma.

XLA patients may develop autoimmune diseases such as autoimmune arthritis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and inflammatory bowel disease. Inflammatory bowel diseases are difficult to control and often cause weight loss and chronic malnutrition. These patients also have an increased risk of developing tumors, in particular gastrointestinal malignancies[11].

Patients with XLA have no ability to develop an antibody response to any vaccine. There is no contraindication to immunization with inactivated vaccine, but oral polio vaccine and all other live attenuated vaccines are absolutely contraindicated, because they may cause vaccine-related infections[12].

In the case presented, the history of recurrent bacterial infections, bronchiectasis, hypogammaglobulinemia, B cells deficiency (CD20 - 0.25%), absence of palpable lymph nodes and hypoplastic tonsils suggested the diagnosis of XLA, confirmed by the presence of mutation in BTK gene.

Despite intense investigation for all the known causes of bronchiectasis, a large proportion of patients will still have idiopathic disease. An even more detailed immunological assessment of patients with idiopathic bronchiectasis combined with investigations for novel gene defects and polymorphisms will probably reveal a range of minor defects that affect immune function in a significant proportion of these patients. It could be predicted that an increasing number of immunodeficiencies associated with bronchiectasis will be identified in the future.

Patients with severe infections from infancy should be evaluated carefully for immunodeficiency diseases, because a late diagnosis and treatment can result in severe illness or death[6,13,14]. The success of obtaining a better quality of life for patients with humoral PIDs is the early diagnosis and the early starting of complex treatment (antibiotics, immunoglobulin replacement therapy and bone marrow / hematopoetic cell transplantation).

The appropriate treatment for XLA with human immunoglobulin therapy (i.v. or through a subcutaneous pump, 400-600 mg/kg every 3-4 weeks, maintaining a serum level of IgG at 500-800 mg/dl) and antibiotics may delay the development and also influence the natural course of bronchiectasis.

Conclusion

There is a wide range of conditions that can cause bronchiectasis and sometimes establishing the etiology of bronchiectasis can be a real challenge for caregivers, especially in case of rare diseases.

The presented case emphasizes that young patients with recurrent infections and bronchiectasis should be carefully evaluated for immunodeficiency diseases, because the correct diagnosis could improve the treatment and prognosis. ■

References

1. Brown J, Baxendale H, Floto R. Immunodeficiencies associated with bronchiectasis. *Eur Respir Mon* 2011, vol. 52, 178–191.
2. Gathmann B, Binder N, Ehl S, Kindle G. ESID Registry Working Party. The European internet-based patient and research database for primary immunodeficiencies: update 2011. *Clin Exp Immunol.* 2012, 167(3):479-9.
3. Kuts L. Clinical Immunology: Primary Immunodeficiency: study guide. Sumy State University, 2014, p. 165.
4. Toth B, Volokha A, Mihas A, et al. Genetic and demographic features of X-linked agammaglobulinemia in Eastern and Central Europe: a cohort study. *Mol Immunol.* 2009, 46(10):2140-6.
5. Sinitina L, Fuior I, Contribuții în morfogeneza unor imunodeficiențe congenitale. Buletin de perinatologie. Chișinău, 2006, vol 1, p. 40-45.
6. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency in children: delayed diagnosis despite typical clinical presentation. *J Pediatr.* 2009, 154:888-94.
7. Obregon R, Lynch D, et al. Radiologic findings of adult primary immunodeficiency disorders. Contribution of CT. *Chest.* 1994; 106:490–495.
8. Al-Herz W, et al. Primary Immunodeficiency Diseases: An Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Frontiers in Immunology. 2014; 5:1-13.
9. www.esid.org /Working-Parties/Registry/Diagnosis-criteria.
10. Mohiuddin MS, Abbott JK, Hubbard N, Torgerson TR, Ochs HD, Gelfand EW. Diagnosis and evaluation of primary panhypogammaglobulinemia: a molecular and genetic challenge. *J Allergy Clin Immunol.* 2013; 131:1717-8.
11. Brosens L, Tytgat K, et al. Multiple colorectal neoplasms in X-linked agammaglobulinemia. *Clin Gastroenterol Hepatol.* 2008; 6(1):115-9.
12. ACIP General Recommendations on Immunization.Vaccination of Persons with Primary and Secondary Immune Deficiencies. Jan 2011.
13. Nuță C, Gherghina I. Boala Bruton – prezentare de caz și comentarii din literatură. *Revista Română de Pediatrie.* 2013; vol. LXII, nr. 3, 306-312.
14. Sigmon JR, Kasasbeh E, Krishnaswamy G. X-linked agammaglobulinemia diagnosed late in life: case report and review of the literature. *Clin Mol Allergy.* 2008; 6:1186/1476-7961-6-5.
15. Notarangelo L, Plebani A, et al. Genetic Causes of Bronchiectasis: Primary Immune Deficiencies and the Lung. *Respiration.* 2007; 74:264–275.