A Case of X-Linked Agammaglobulinemia Presenting with Recurrent Pneumonia and Bronchiectasis

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Abstract

Recurrent infection especially recurrent sinopulmonary tract infection is a typical clinical condition for referral to pediatrician. Patients with recurrent pneumonia should be evaluated for underlying diseases including asthma, congenital heart diseases, gastroesophageal reflux, foreign body aspiration, structure anomalies, cystic fibrosis and immunodeficiency. Our one patient with recurrent pneumonia had hypoglobulinemia, low number of circulating B cell with deficiency of CD19 B cell, absence of tonsils and recurrent pneumonia requiring hospitalization. PCR and sequencing revealed mutation of Bruton tyrosine kinase (Btk) gene on Xq22, suggested that he had X-linked agammaglobulinemia (XLA). The appropriate treatment of XLA was good hygiene care, treatment of infection and prophylactic therapy with intravenous immunoglobulin. This report should alert the pediatrician and general practitioners to consider the diagnosis of primary immunodeficiency diseases. The early diagnosis and proper management can prevent comorbidity diseases and improve quality of patient's life.

Keywords: Recurrent pneumonia, Bronchiectasis, X-linked agammaglobulinemia

รายงานผู้ป่วย X-Linked Agammaglobulinemia ที่มีประวัติโรคปอดอักเสบชนิดกลับเป็นซ้ำและโรคหลอดลมโป่งพอง

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บทคัดย่อ

การติดเชื้อระบบทางเดินหายใจแบบกลับเป็นซ้ำ เป็นภาวะที่ผู้ป่วยเด็กได้รับการส่งต่อมาพบกุมารแพทย์ โดยผู้ป่วยที่มีโรคปอดอักเสบแบบกลับเป็นซ้ำจำเป็นต้องได้รับการวินิจฉัยแยกโรคต่างๆ ได้แก่ โรคหอบหืด โรคหัวใจพิการแต่กำเนิด ภาวะกรดไหลย้อน ภาวะการอุดกั้นทางเดินหายใจจากสิ่งแปลกปลอม ภาวะการผิดรูปของทางเดินหายใจแต่กำเนิด cystic fibrosis และภาวะภูมิคุ้มกันบกพร่อง

ผู้ป่วยรายนี้ มีประวัติโรคปอดอักเสบแบบกลับเป็นซ้ำ ทำให้ผู้ป่วยต้องเข้ารักษาในโรงพยาบาลหลายครั้ง จากการตรวจร่างกายพบว่าผู้ป่วยไม่มีทอนซิล และการตรวจทางห้องปฏิบัติการพบว่า มีภาวะพร่องอิมมูโนโกลบูลิน (hypoglobulinemia) และพบ B-cell ชนิด CD19 B-cell ลดต่ำมากในเลือด ซึ่งวินิจฉัยโรคโดยการตรวจยืนยันทางพันธุกรรม พบว่า ผู้ป่วยรายนี้มี mutation ของ Bruton tyrosine kinase (Btk) gene บน chromosome Xq22 จึงเข้าได้กับโรค X-Linked Agammaglobulinemia (XLA) การรักษาโรคนี้ ขึ้นอยู่กับการดูแลสุขอนามัยที่ดีของผู้ป่วย รักษาภาวะติดเชื้อต่างๆ และการให้อิมมูโนโกลบูลินทางเส้นเลือด (intravenous immunoglobulin) เพื่อเพิ่มภูมิคุ้มกันและลดโอกาสการติดเชื้อให้กับผู้ป่วย

การรายงานผู้ป่วยรายนี้เพื่อเป็นประโยชน์แก่กุมารแพทย์และแพทย์ทั่วไปเพื่อให้ตระหนักถึงโรคภูมิคุ้มกันบกพร่องแบบปฐมภูมิ ซึ่งการวินิจฉัยโรคได้เร็ว และให้การรักษาอย่างถูกต้องเหมาะสม จะลดภาวะแทรกซ้อนของโรคและเป็นการเพิ่มคุณภาพชีวิตผู้ป่วยให้ดีขึ้น

คำสำคัญ: ปอดอักเสบติดเชื้อชนิดกลับเป็นซ้ำ, ภาวะภูมิคุ้มกันบกพร่องแบบปฐมภูมิ

Introduction

X-linked agammaglobulinemia (XLA) or Bruton's disease is a humoral immunodeficiency disease characterized by low levels or absence of serum immunoglobulins[1]. Bruton described the disease since 1952[2]. The gene mutation encoded tyrosine kinase (Bruton's tyrosine kinase or *Btk*), located at the long arm of X-chromosome. The absence of *Btk* protein or lack of function results in the arrest of B-cell development, affecting the early stages of B-cell differentiation and profound hypogammaglobulinemia[3]. The worldwide incidence of XLA range was estimated from 1:100,000 to 200,000 live births[4-5]. World allergy organization (WAO) reported the largest study of patients with XLA on 783 patients from 40 centers around the world in 2019. The delays diagnosis was the highlighted problem, reporting that 34% of patients were diagnosed at the age of more than 24 months and 39% of the centers did not perform genetic studies. 41% of mortality rate were resulted from acute and chronic lung diseases[5]. Reports of patients with XLA in Thailand past second decade from Siriraj hospital, Ramathibodi hospital and Chiang Mai university were 6, 2 and 6 patients[6-8].

The onset of recurrent bacterial infection typically begins between 6 and 12 months of age, when maternal antibodies through the placenta are reduced below protective levels. The sinopulmonary tract is the most frequent site of infection, causing otitis media, sinusitis, bronchitis, and pneumonia. Other sites of infection include septicemia, meningitis, encephlitis, meningoencephalitis, osteomyelitis and septic arthritis. The most common organism is pyogenic or encapsulated bacteria such as *Haemophilus influenza, Streptococus pneumoniae* and *Staphylococcus aureus.* Because the cellular immunity is generally intacted, the viral infection, fungal infection and tuberculosis are normally resistances. Exceptionally, the enteroviruses can cause the infection in patients with XLA[9-10].

Early recognized patients with recurrent infection and early diagnosis, appropriate antibiotics treatment of infection, replacement therapy with intravenous immunoglobulin (IVIG) has improved prognosis of patients with XLA[5]. Chronic infection, especially enteroviral infection and sinopulmonary tract infection is the most complication in XLA patients[9-10]. Recurrent pneumonia usually causes morbidity and mortality, where inadequate treated pulmonary infections finally cause bronchiectasis. Definition of recurrent pneumonia is two or more episodes of pneumonia in a year, or 3 episodes in any time period[11].

The author report a case of XLA patient with recurrent pneumonia and bronchiectasis that is typical of the late diagnosed primary immunodeficiency diseases. This report showed the importance of evaluating patients with recurrent infection. Early diagnosis and proper treatment determine the patient's prognosis and quality of life.

Case report

A 6 year and 10 month old boy was present with fever, cough and dyspnea. He had previously been hospitalized for pneumonia four times and had acute otitis media one time. Then, he had been suffering from upper respiratory tract infection 1-2 times per month. The first hospitalization for pneumonia was at the age of 18-month old. Another hospitalization was 3-year old, 4-year old, 5-year and 5-month old. He was the first child of non-consanguineous parent and had one sister who has different father. He was born 2,800 gm at term with normal delivery. There was no family history of immunodeficiency.

The physical examination was dyspnea, suprasternal and intercostal retractions and decrease breath sound at right lung. He had a high-grade fever (39°C). His weight was the 10th percentile. He had injected pharynx with absent tonsils. There were not palpable lymph nodes. Laboratory tests were as follows: white blood cells 22,500/mL (neutrophils 79.6%, lymphocytes 15.9% and mononucleosis 4.2%); hemoglobin 11.6g/dL; platelets 655,000/mL. Biochemical and urine analysis were within normal levels. His chest radiographic finding showed bilateral interstitial

infiltration with blunt of right costophernic angle. The film right lateral decubitus showed fluid level 1.4 cms(Fig.1). Thoracentesis was done to remove serosanguinouse fluid 74 ml. The result of cultures of blood, sputum and pleural fluid were also negative.

He had received cefotaxime and azithromycin with the diagnosis of pneumonia. His physician had consulted pediatric pulmonologist for evaluation recurrent pneumonia. The pulmonologist suggested performing chest computerized tomographic. His computer tomography finding revealed the right middle lobe atelectasis with bronchiectasis without demonstrable obstruction in segmental bronchi (Fig.2). The incentive spirometer (Cliniflow meter®) was used to help him improve the lung function. Therefore, the history of recurrent pneumonia requiring hospitalization, otitis media and absence of tonsils had determined immune deficiency status. The secondary immune deficiency was excluded; Anti-HIV test was negative. Pediatric allergist and immunologist suggested evaluation of immunological laboratory tests. The serum immunoglobulin(Ig) was as follows: IgG 98 mg/dL (normal range:923±256), IgA 6.5 mg/dL(124±45) and IgM levels 16.2 mg/dL(124±45) and IgG subclass: IgG_1 46 mg/dL(269-1120), IgG_2 26 mg/dL(30-630), IgG_3 8.2 mg/dL(40-250), IgG_4 0.6 mg/dL(11-620). Flow cytometric analysis of peripheral blood reveals mixed population of lymphocyte subset as shown in Table 1.

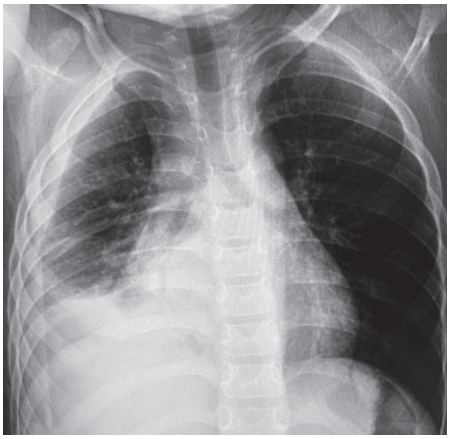

Figure 1: Chest radiography showing bilateral interstitial infiltration with blunt of right costophernic angle and effusion.

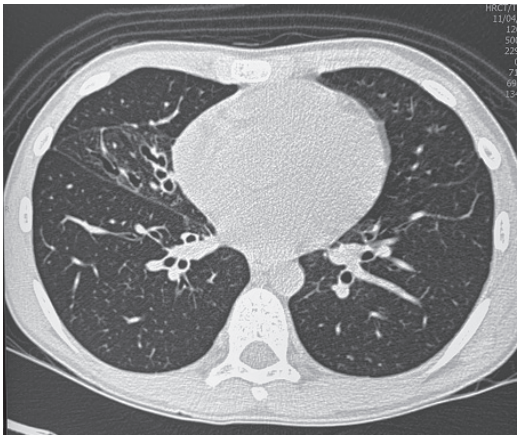

Figure 2: Computer tomography finding revealed the right middle lobe atelectasis with bronchiectasis without demonstrable obstruction in segmental bronchi.

Table1:

Flow cytometric of analysis of lymphocyte subset of patient.

Lymphocyte subset	% of total lymphocyte	Reference range	Absolute count (K/ul)	Reference range
Total T-cell (CD3+)	91.34	(66-76)	5.54	(1.4-2.0)
CD4+ T-cell (CD3+CD4+)	37.78	(33-41)	2.29	(0.7-1.1)
CD8+ T-cell (CD3+CD8+)	48.11	(27-35)	2.92	(0.6-0.9)
NK-cell (CD3-CD16+CD56+)	7.24	(9-16)	0.44	(0.2-0.3)
B-cell (CD19+)	0.31	(12-22)	0.02	(0.3-0.8)

This case showed markedly low serum immunoglobulin level and low levels of B cell (CD19+) in peripheral circulation (0.31%) by flow cytometric analysis. The genetic laboratory report showed a hemizygous nucleotide substitution from C to T (CGA to TGA) at nucleotide 1558 in exon 15 (c.1558C>T) of the *Btk* gene was identified, resulting in an amino acid change from Arg to stop at codon 520 (p.R520X) (Fig.3). A missense mutation **p.R520X** was identified in the patient, confirming the diagnosis of Bruton hypogammaglobulinemia. Carrier testing in mother was no pathogenic mutation.

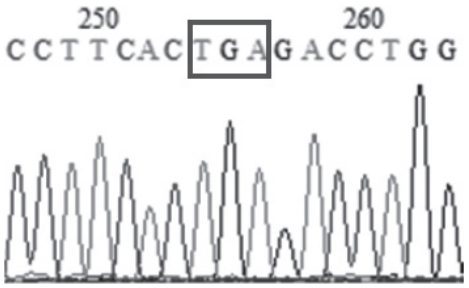

Figure 3: PCR amplification and sequencing of all 19 coding exons of BTK gene.

He was received intravenous immunoglobulin (IVIG) replacement therapy 400 mg/kg on this admission. At the second week of admission, he was totally recovered and discharged with a treatment schedule of monthly IVIG injections in dosages of 400 mg/kg. The vaccination for preventing invasive pneumococcal disease and influenza infection were received.

Discussion

The age of onset of infection in XLA patients was between 13 and 40 months was 48.3% and after 40 months of age was 31.7%[9]. Present case has begun onset of symptoms at 18-month old and recurrent respiratory tract infection once a year. The study from the northern part of Thailand also reported onset of symptoms ranged from 1 to 5 (mean 2.5) years, and the age at diagnosis ranged from 5 to 11 (mean 7.3) years[8]. The presenting manifestation surveys around the world showed the lower respiratory tract infection more than 65% of XLA patients[5,9-10]. Patients with recurrent pneumonia should be evaluated for underlying diseases including asthma, congenital heart diseases, gastroesophageal reflux, foreign body aspiration, structure anomalies, cystic fibrosis and immunodeficiency[11]. Hypoglobulinemia, low number of circulating B cell with deficiency of CD19 B cell, absence of tonsils and recurrent pneumonia requiring hospitalization suggested that our patient had XLA. Recurrent pneumonia was predominant manifestation in most complication of XLA patients[8-10]. Trakultivakorn et al., reported that bronchiectasis was presented in five out of six patients, possibility reflecting the delay of diagnosis[8].

XLA is a rare genetic disorder with the B cells development which is arrested during differentiation. The diagnosis has been genetic analysis of the *Btk* gene. Defects in the *Btk* gene affect the early B cell differentiation[12]. The genetic defect has been located on the midportion of X chromosome (Xq22). Obligate carrier has been usually testing carrier gene[13].

The appropriated treatment of XLA was supportive care, good hygiene care, appropriated antibiotic for acute and chronic infection and prophylactic therapy with IVIG[1,3]. Recommended dosage was a range from 300 to 600 mg/kg every 4 weeks for patients with antibody deficiency[14]. Our patient was free serious infections while on 400 mg/kg IVIG replacement therapy every 4-5 weeks. Also, he was received vaccination for prevent sinopulmonary tract infection.

Conclusion

Recurrent pneumonia and/or recurrent sinopulmonary tract infection are a typical clinical condition for referral to pediatrician. The physical finding of absent tonsils and lymph nodes are the most characteristic features of patient with defect in B-cell development. The male patients who had many episodes of sinopulmonary tract infection and hypoplasia of lymphoid tissue should be considered the diagnosis of XLA and confirmed by mutation analysis. This report should alert the

pediatrician and general practitioners considering the diagnosis of primary immunodeficiency diseases. The early diagnosis and proper management can prevent comorbidity diseases, decrease in missing school day and improve quality of life of patients.

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