CASE REPORT

Bagcilar Med Bull 2021;6(1):88-91
DOI: 10.4274/BMB.galenos.2020.09.062

A Case of Severe Spontaneous Pneumomediastinum in Acquired Immunosuppressed Child with Respiratory Syncytial Virus and Human Bocavirus Co-infection

Solunum Sinsityal Virüs ve İnsan Bokavirüs Ko-enfeksiyonu Olan Edinilmiş İmmün Yetmezlikli Çocuk Olguda Ciddi Bir Spontan Pnömomediastinum Olgusu

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Abstract

Spontaneous pneumomediastinum is an uncommon, benign, and self-limiting disease based on the presence of free air in the mediastinal cavity. It can occur after a forced Valsalva's maneuver due to a cough, emesis or during an asthma exacerbation. We present a 4-month-old girl infant with an autoimmune hemolytic anemia and lymphopenia, who was admitted to the pediatric intensive care unit due to respiratory distress. A suspected pneumomediastinum image on chest X-ray was documented by the chest tomography. A polymerase chain reaction of the nasopharyngeal secretions was positive for a respiratory syncytial virus and human bocavirus. Additionally, she was examined for an immune deficiency due to her lymphopenia. The patient required mechanical ventilatory support for 26 days. She was treated with antibiotics, antiviral, and antifungal agents and corticosteroids. Intravenous immunoglobulin, trimethoprim sulfamethoxazole, and fluconazole prophylaxis were continued because of the ongoing lymphopenia. At the end of five weeks, the patient was discharged with a normal lymphocyte count and without any respiratory distress. In immunosuppressed patients, respiratory diseases may be severe and long. Therefore, complications including pneumomediastinum can be seen more frequently in this group of patients.

Keywords: Human bocavirus, immunodeficiency, respiratory syncytial virus, rituximab, spontaneous pneumomediastinum

Öz

Spontan pnömomediastinum, mediastinal kavitede serbest hava varlığına dayanan, nadir görülen, iyi huylu ve kendi kendini sınırlayan bir hastalıktır. Öksürük, kusma veya astım alevlenmesi nedeniyle yapılan zorunlu bir Valsalva manevrasından sonra ortaya çıkabilir. Bu olgu sunumunda, solunum sıkıntısı nedeniyle pediyatrik yoğun bakım ünitesine yatırılan, otoimmün hemolitik anemi ve lenfopenisi olan 4 aylık bir kız çocuğunu sunduk. Akciğer grafisindeki şüpheli pnömomediastinum görüntüsü akciğer tomografisi ile belgelendi. Nazofarengeal salgıların polimeraz zincir reaksiyonu, solunum sinsityal virüsü ve insan bokavirüsü için pozitifti. Hasta ek olarak lenfopeni nedeniyle bağışıklık yetersizliği açısından da tetkik edildi. Hasta 26 gün mekanik ventilatör desteğine ihtiyaç duydu. Bu sırada antibiyotik, antiviral ve antifungal ajanlarla ve kortikosteroidlerle tedavi edildi. Devam eden lenfopeni nedeniyle intravenöz immünoglobulin, trimetoprim sulfametoksazol ve flukonazol profilaksisi kullanıldı. Bağışıklık sistemi baskılanmış hastalarda, solunum yolu hastalıkları şiddetli ve uzun sürebilir. Ayrıca, pnömomediastinum gibi komplikasyonlar bu hasta grubunda daha sık görüldüğünden dikkatli olmakta fayda vardır.

Anahtar kelimeler: İmmün yetmezlik, insan bokavirüsü, rituximab, solunum sinsityal virüsü, spontan pnömomediastinum

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One of the authors of this article (EŞ) is a member of the Editorial Board of this journal. She was completely blinded to the peer review process of the article.

Cite this article as: Koçoğlu Barlas Ü, Kasap N, Akçay N, Petmezci MT, Devecioğlu Ö, Şevketoğlu E. A Case of Severe Spontaneous Pneumomediastinum in Acquired Immunosuppressed Child with Respiratory Syncytial Virus and Human Bocavirus Co-infection. Bagcilar Med Bull 2021;6(1):88-91.

Introduction

Spontaneous pneumomediastinum (SPM) is defined by the presence of free air in the mediastinum. It was reported by Hammam for the first time. It is also rare at the pediatric age (1). The most common-known etiologic cause of pneumomediastinum (PM) is trauma, but in children, it occurs after a forceful Valsalva's maneuver due to cough, emesis or an asthma exacerbation (2).

In this article, we present a 4-month-old girl patient with an autoimmune hemolytic anemia and lymphopenia. She was admitted to our pediatric intensive care unit (PICU) due to an SPM which occurred secondary to the respiratory syncytial virus (RSV) and human bocavirus (HBoV) co-infection. Additionally, she was examined for an immune deficiency due to the lymphopenia.

Case Report

A 4-month-old girl infant was admitted to our emergency room with a 5-day history of respiratory distress. Her heart rate was 165 beats/min, respiratory rate was 64/min, and her blood pressure was 100/88 mmHg. Venous blood gas analysis showed pH 7.43, pCO_2 37.4 torr, HCO_3 24.3,white blood cell count revealed lymphopenia (lymphocyte count: 870 mL, normal: 3.190-10.626 mL) and direct coombs was negative. A suspected PM image on the chest X-ray was documented by a chest tomography (Figure 1, 2). The child was referred to our PICU because of her worsening clinical condition.

In the PICU, she was intubated due to a hypoxic respiratory failure. Her medical history revealed that she had been treated with three days of pulse methylprednisolone and once with rituximab (RTX) treatment, for autoimmune hemolytic anemia last month. When she was admitted to our hospital, she was on methylprednisolone therapy at a dose of 2 mg/kg/day. The patient was examined for lymphopenia with immunoglobulins, alpha 1 antitrypsin level, lymphocyte subgroups, autoimmune disorders, cystic fibrosis, and metabolic disease screening. The patient and her family were screened for tuberculosis because of its frequency in our country.

The following day, a diagnosis of RSV and HBoV co-infection was made by reverse transcriptase-polymerase chain reaction (PCR) on a nasopharyngeal swab. The patient required mechanical ventilatory support for respiratory failure for two weeks. With the continuation of PM sign on control chest tomography, she required mechanical ventilatory support for two more weeks. Congenital metabolic diseases and autoimmune disorders were ruled out with normal urine and blood aminoacids and negative autoimmune markers. The alpha 1 antitrypsin level was normal (143 mg dL, normal: 111-297 mg dL). Serum immunoglobulin levels were within a normal range (IgG: 717 mg dL, normal: 294-1.165 mg dL, IgA: 14.5 mg dL, normal: 13.5-72 mg dL, IgM: 58.5 mg dL, normal: 33-154 mg dL). Absolute lymphocyte counts were 590 cells µL and lymphocyte phenotyping demonstrated $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16^+56^+$ lymphopenia [$CD3^+$ cells µL: 499 (1.933-7.362), $CD4^+$ cells µL: 295 (1.262-5.269), $CD8^+$ cells µL: 204 (498-252), $CD19^+$ cells µL: 0, $CD16^+56^+$ cells µL: 49 (95-1.740)]. Due to T^- B^- NK^- (natural killer) severe combined immunodeficiency phenotypic presentation, adenosine deaminase (ADA) deficiency was considered

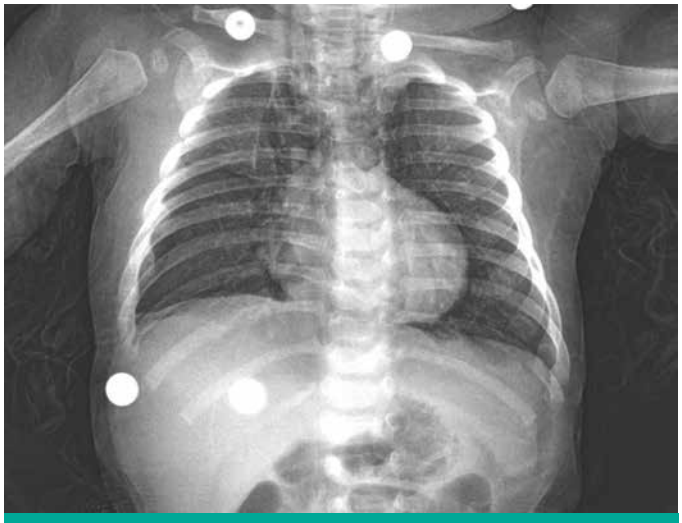

Figure 1. Chest X-ray of the patient

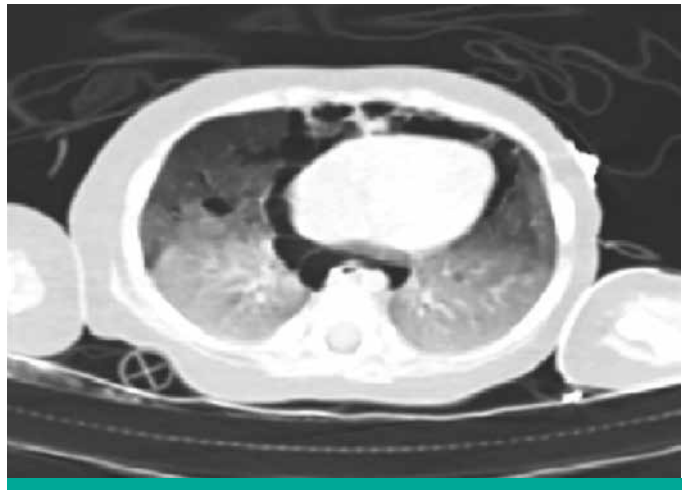

Figure 2. Chest CT scan of the patient
CT: Computed tomography

and excluded by the normal ADA enzyme levels. Because of severe viral infections and autoimmunity, signal transducers and activators of transcription (STAT1) mutation and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) mutations were considered; *STAT1* gen sequencing was normal and LRBA protein expression by flow cytometry was detected as comparable to healthy controls. Whole exome sequencing was considered for screening monogenic diseases (e.g. MALT1 def., CARD11 def., BCL-10 def. etc.) that could be in a differential diagnosis, followed by a primary autoimmune hemolytic anemia and immunodeficiency. Intravenous immunoglobulin, trimethoprim sulfamethoxazole, and fluconazole prophylaxis were continued because of the ongoing lymphopenia. Tuberculosis PCR was negative.

After 26 days of intubation, she continued on a non-invasive mechanical ventilation with bilevel positive airway pressure) (epap: 6 cm H_2O, ipap: 11 cm H_2O) and then a non-rebreather mask with oxygen. At the time of discharge (48th day), her lymphocyte count was 2.240 mL (1.880-5.390 mL), but the lymphocyte phenotyping still demonstrated $CD19^+$ lymphopenia [$CD3^+$ %: 54.6 (51-85.3), $CD4^+$ %: 29.2 (29.7-63.6), $CD8^+$ %: 21.7 (11.5-33.7), $CD19^+$ %: 0.04 (7.9-53.6), $CD16^+56^+$%: 40 (2.3-17.2)], low recent thymic emigrant cells [RTE: %: 33 (63-90)], naif $CD4^+$ T cells [42.2% (60.4-95.5) and high memory $CD4^+$ T cells [50.3% (8.9-37.7)]. No mutation was detected in the *ADA* gene analysis which was performed before discharge.

Discussion

SPM might be triggered by respiratory tract infections, asthma, esophageal rupture, foreign body aspiration, and several circumstances involving a Valsalva maneuver (3). The incidence of SPM in childhood is between 1/8.000 and 1/15.000 in the emergency department admissions, and more frequent in male gender (4). Our patient was a girl and had no history of trauma, foreign body ingestion, or aspiration. According to the literature, emphysema is the most common finding in physical examination, but our patient had only respiratory distress (5). Therefore, although SPM can generally be diagnosed by chest graphy, chest tomography was needed twice for diagnosis in our case (6).

Lower respiratory tract infections such as bronchiolitis and viral pneumonia are the leading causes of hospitalization for infants. Prematurity, chronic pulmonary disease, and immune deficiency are the risk factors for these diseases. It is known that RSV is the most common acute pathogen which causes up to 75% of cases (7). However, RSV infection's potentiality for SPM is low, and there is little evidence in the literature (8). HBoV is another pathogen that is frequently found in hospitalized children under two years of age. The most challenging aspect for the patient was the ongoing lymphopenia during the treatment. This situation led to a prolonged hospitalization in contrast to the literature. The mean hospitalization period of SPM cases is between 4 and 6 days in the literature, but our case stayed for 48 days in PICU (9). Serum immunoglobulin levels were normal, but lymphocyte subsets revealed lymphopenia of T, B, NK cells. Although pulmonary diseases such as pneumonitis and pulmonary alveolar proteinosis are more common in patients with ADA deficiency (10), we excluded it by normal ADA enzyme levels and then normal gen analysis. STAT1 mutation and LRBA mutations were considered, *STAT1* gene analysis and LRBA expressions were normal. Due to a primary autoimmune hemolytic anemia and immunodeficiency, whole exome sequencing was attempted for monogenic diseases that could be in differential diagnosis. Since the patient had an absolutely normal lymphocyte count with normal lymphocyte subsets during the neonatal period and at the time of discharge, a history of infection, using immunosuppressive treatments such as RTX and CS for autoimmune hemolytic anemia and persistent lymphopenia, along with these medications, may suggest a secondary immunodeficiency rather than a primary one. In a meta-analysis of 21 studies, RTX was found to be a safe and effective therapy for autoimmune hemolytic anemia (11). Hypotension, fever and chills are the most common infusion-related side effects. D'Amico et al. (12) also investigated the effects of RTX on demyelinating diseases and found lymphopenia in one patient. Baris et al. (13) observed a lymphocyte subset changing in children diagnosed with nephrotic syndrome treated with corticosteroids (CSs), and it showed that T-cells were suppressed very early in the CS treatment and more susceptible to CSs more than B-cells. The change of B-cell subtypes shows a prolonged effect of CSs on B-cells, which may alter antibody production even after three months of CSs cessation (13).

At the follow-up of patient, clinical improvement with the decreasing infection and progress in lymphopenia confirmed the development of reversible secondary immunodeficiency.

Conclusion

In immunosuppressed patients with PM, respiratory diseases may be severe and long. When investigating the cause of immunodeficiency, the patient's previous diagnosis and treatment should be reviewed.

Consent was obtained from the family to use information about the patient.

Ethic

Informed Consent: Consent was obtained from the family to use information about the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Follow-up of the case: Ü.K.B., N.A., M.T.P., E.Ş., Literature review: N.K., N.A., M.T.P., Ö.D., E.Ş., Writing: Ü.K.B., N.K., M.T.P., Ö.D., E.Ş.

Conflict of Interest: The authors declare that there is no conflict of interest with regard to this manuscript.

Financial Disclosure: No financial support was received from a person or a company for writing this case report.

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