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APDS Disorder Masked Under Asthma And Tuberculosis: A Rare Case Report

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Abstract

Background: Activated Phosphoinositide 3 Kinase Delta Syndrome (APDS) is a rare condition that affects the immune system. It is caused by specific genetic mutations that lead to increased activity of PI3Kδ. One of the main features of this syndrome is recurrent infections in the ear, sinuses, upper and lower respiratory tract. Lymphoma and complications from stem cell transplant are the primary factors contributing to mortality in APDS patients, with mortality rates of 47.6% and 15.6% respectively.

Case: The study presents a case of 24-year-old female with medical history of recurring infections and asthma that was diagnosed at the age of 8. At the tender age of 20, her health began to decline as she faced a series of challenging infections started with Aspergillus, followed by Tuberculosis, then COVID-19, and finally Nocardia.

Discussion: An investigation into primary immunodeficiency was carried out. The immunoglobulin levels were found to be within the normal range, ruling out Common Variable Immunodeficiency (CVID). An analysis of immunochemistry data indicated a significant reduction in the proportion and total count of Natural Killer cells. Although the occurrence of Aspergillosis with a secondary Tuberculosis infection is not frequently observed in APDS, it was indeed identified in this specific case.

Conclusion: This case emphasises the challenging issue of persistent occurrence of opportunistic infections such as nocardiosis, coupled with the development of antibiotic resistance due to prolonged usage making the diagnosis and treatment tough.

Keywords – APDS, Immune system, Asthma, Infections

I. INTRODUCTION

Activated Phosphoinositide 3 Kinase Delta Syndrome (APDS) is a rare autosomal dominant inborn error of immunity that arises from a gain-of-function mutation in the genes responsible for encoding phosphoinositide 3-kinase □(P13K□). The incidence of APDS is extremely rare, with only 1-2 cases per million reported globally. Most affected individuals have been identified in the regions of China and Japan. P13K□ is predominantly found in leukocytes and plays a crucial role in the growth, specialization, and development of these cells. Genetic mutations result in increased phosphorylation of AKT/mTor proteins by P13K, resulting in

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compromised cell proliferation and the initiation of early cell death. APDS also has an impact on humoral immunity as it hinders class switching and decreases the presence of memory B-cells [1]. Respiratory symptoms were found to be predominant among APDS patients, despite the heterogeneity in their clinical manifestations [2]. Early manifestations of the disease included infections of the ear, sinuses, and upper and lower respiratory tract. Patients with APDS were discovered to have a high susceptibility to hematological malignancies and viral infections, including Epstein Barr Virus infection (EBV) and Cytomegalovirus infection (CMV) [3]. The utilization of the P13K/AKT pathway by Varicella Zoster Virus(VZV) for its survival and replication has been documented leading to increased risk of HPV infection in these patients [3]. Additionally, there is evidence of compromised humoral immunity, which can result in the development of lymphadenopathy and splenomegaly. The blood reports in APDS patients present an elevated count of CD3+/CD8+CD57+ (senescent T cells). APDS is frequently misdiagnosed as Hyper IgM Syndrome or Common Variable Immunodeficiency (CVID) because of the similarities in their clinical presentation. Gene sequencing is instrumental in the accurate diagnosis of APDS. Available treatment options include antibiotic prophylaxis, immunoglobulin replacement therapy, and hematopoietic stem cell transplantation (HSCT). These interventions have demonstrated efficacy in decreasing the occurrence of severe infections and lymphomas. Ongoing research is being conducted to evaluate the effectiveness of P13K□ inhibitors, such as Leniolisib [1,3].

II. Case Presentation

On 13 August 2020, 24-year-old female patient, with past medical history of asthma, recurrent infections and sinusitis visited the clinic with the chief complaints of high fever, cough, headache, and fatigue.

Her Asthma was diagnosed at the age of 8 and is currently on medication. Her mother attributed the cause for her daughter's recurrent infections from early childhood to nutritional deficiency during her pregnancy. Patient's father has dextrocardia without any other pathology. Patient's height is 168 cm and weight 48 kg, resulting in BMI of 17 classifying as underweight.

The patient was relatively healthy during the years 12-19 of her life apart from asthma and occasional seasonal infections but her health started deteriorating at the age of 20 when she was diagnosed with and treated for multiple infections every other month. The series of infection includes Aspergillus infection, followed by Tuberculosis, Covid 19 and Nocardia.

III. Clinical Findings

Blood tests and culture, flow cytometry, and chest CT scan were ordered to the patient. Lymphocyte subset enumeration via flow cytometry revealed low absolute count and percentage of CD56/16+ (Natural Killer cells) but was otherwise normal. Table 1 shows the patient's reports of flow cytometry.

Table 1: Lymphocyte subset enumeration via flow cytometry

Diagnostic tests	**Results**	**Unit**	**Reference range**
Total leukocyte count (TLC)	5.7	10^3/µL	4.0 - 11.0
Absolute lymphocyte count	1.40	10^3/µL	1.0 - 3.0
Absolute CD3 Count (T cells)	1187.0	Cells/µL	527 - 2846
CD3 %	81.26	%	49 - 81

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Absolute CD19 count (B cells)	194	Cells/µL	78 - 899
CD19 %	13.26	%	7 - 23
Absolute CD56/16+ count (NK cells)	54	Cells/µL	67 - 1134
CD56/16 %	3.67	%	6 - 29
Absolute CD3+ CD4+ Counts	664	Cells/µL	332 - 1134
CD4 %	45.47	%	28 - 51
Absolute CD3+ CD8 + counts	482	Cells/µL	170 - 811
CD8 %	32.97	%	12 - 38
CD4/CD8 ratio	1.37		0.7 - 3.5

IV. DIAGNOSTIC ASSESSMENT

The patient began experiencing repeated upper respiratory tract infections during adolescence. When she was 20 years old, she received a diagnosis of aspergillosis complicated by secondary tuberculosis (TB) infection. This diagnosis was confirmed through bronchoalveolar lavage and high-resolution CT scan, which revealed the presence of multiple areas of centrilobular micronodules with a linear branching pattern that resembled a budding tree (Image1). Blood samples were collected for culture, antibiotic sensitivity, and resistance testing, and the necessary treatment was promptly started. The patient experienced further infections, such as COVID-19 and Nocardia, indicating a potential immunodeficiency condition.

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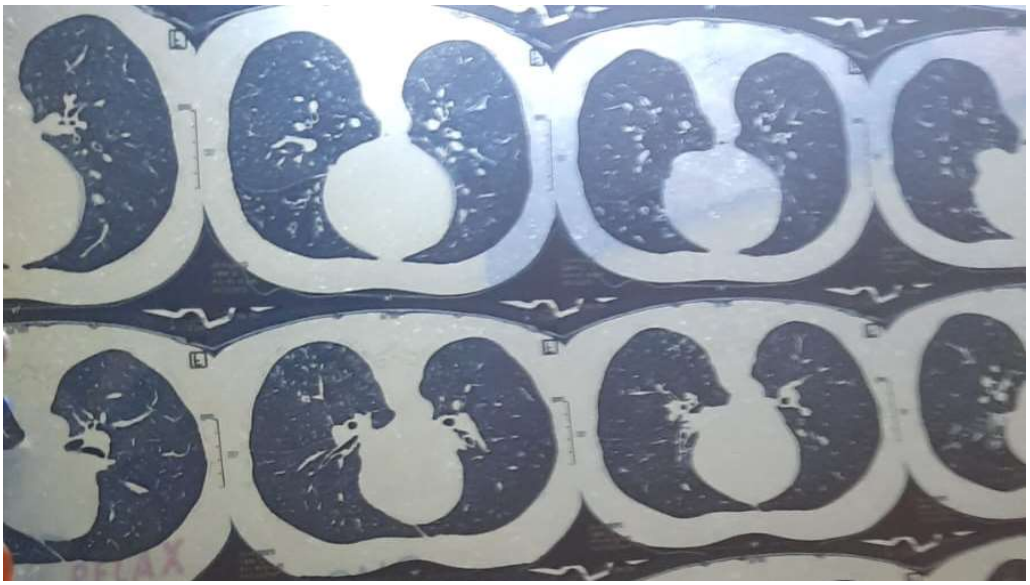

Image 1: CT scan showing the presence of multiple areas of centrilobular micronodules with a linear branching pattern that resembled a budding tree.

An investigation into primary immunodeficiency was carried out. Immunoglobulin levels were within the normal range, with a slight elevation in IgE levels attributed to fungal infections. This finding effectively eliminates the possibility of common variable immunodeficiency (CVID). An analysis of immunochemistry data indicated a significant reduction in the percentage and absolute numbers of natural killer (NK) cells. Regular blood tests were conducted to culture and determine the antibiotic sensitivity and resistance, to ensure the correct treatment of opportunistic infections. Patient was recommended to undergo genetic counselling, considering her father's history of dextrocardia.

V. DISCUSSION

ADPS, an autosomal dominant disorder of immune system, usually presents with recurrent respiratory tract infections. The most common organisms causing infections include EBV, CMV, and VZV among the viruses, Streptococcus pneumoniae, Haemophilus influenza, and Staphylococcus aureus among the bacteria and Candida albicans amongst the fungal pathogens [4]. Although Aspergillosis with a secondary TB infection is not commonly seen in ADPS, it was identified in our case. Qiu et al described the increased susceptibility of Mycobacterium tuberculosis in pediatric patients diagnosed with APDS [5]. The challenging situation in this case was continuous opportunistic infections like nocardiosis and resistance to antibiotics with chronic usage.

The treatment options for APDS include prophylactic antibiotics, immunoglobulin replacement therapy (IRT), immunosuppressive agents, and HSCT (Hematological stem cell transplant). Patients with APDS with recurrent bacterial infections have antibody deficiency. IRT therapy has been shown to decrease recurrent infections in such patients [4]. In this case, there is a decrease in the percentage of NK cells. Garcia et al described that NK Cell function can be partially restored with the usage of Rapamycin in APDS patients [4]. HSCT has shown to improve clinical symptoms in younger patients, although there was 10-20% risk of mortality due to complications, so HSCT should be reserved for patients who do not respond to conventional therapies [4]. The common causes of mortality in APDS patients were found to be lymphoma and complications from HSCT with mortality rates of 47.6% and 15.6% respectively [5].

Despite suffering from recurrent infections from birth, our patient was diagnosed with APDS at the age of 24.

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VI. RESULTS

The patient has commenced treatment for the ongoing infection. The patient's TB infection was also addressed through a six-month regimen of anti-tubercular drugs. She was consistently observed for any potential infections or adverse reactions to the medications. Continuous monitoring of her vitamin B6 levels and liver and kidney function tests was conducted to assess the effects of the anti TB drugs. Following a six-month regimen of anti-TB medication, her blood cultures report indicated the absence of any active TB infection. The patient's asthma medication was maintained and she was advised to diligently adhere to the safety guidelines to prevent opportunistic infections. Prophylactic vaccines were administered to the patient to protect against streptococcal and HPV infections.

The patient was also informed about other treatment options, such as IRT and HSCT, in case the symptoms worsen. The patient was unprepared for the progress in treatment as she prioritized safety protocols and prophylactic measures.

VII. CONCLUSION

APDS is a rare genetic disorder resulting in a compromised immune system, making individuals more susceptible to various opportunistic infections. The case presented highlights the difficulties encountered in diagnosing and treating the patient, because of prolonged antibiotic use and the presence of underlying asthma and TB infection. Analysing the flow cytometry is crucial in order to eliminate the possibility of immunodeficiency diseases. Blood cultures and CT scan are valuable tools in the diagnostic process and play a crucial role in guiding the treatment plan. It is important to monitor the patient for the potential risk of developing lymphoma. There are several treatment options available in APDS, including IRT, HSCT, immunosuppressive agents, and prophylactic antibiotics and vaccines. The mortality rate among patients with APDS is primarily attributed to lymphoma and the inability of HSCT to effectively address the condition.

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