Novel Genetic Variant of Ataxia Telangiectasia Presenting with Necrotising Pneumonia and Bronchopleural Fistulae at the Age of 4 Years

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ABSTRACT

Ataxia-telangiectasia (A-T) is a genetically inherited disease, which is transmitted as an autosomal recessive disorder. There is a high incidence of consanguineous marriages in our area, so we believe that A-T may have higher incidence. A-T is characterised clinically by triad of cerebellar degeneration, telangiectasia, and immunodeficiency. We are reporting a 4-year girl with a novel genetic variant of AT, which is not reported before in local or international literature. She presented with necrotising pneumonia complicated by bronchopleural fistulae. She was treated successfully with antimicrobials and intravenous immunoglobulins and other supportive measures without surgical intervention.

Key Words: *Ataxia telangiectasia, Necrotising pneumonia, Bronchopleural fistulae.*

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INTRODUCTION

The prevalence of ataxia-telangiectasia (A-T) varies widely. It is estimated that the disease affects between 1 in 40,000 to 1 in 100,000 live births.[1] Recurrent sino-pulmonary infections, progressive ataxia and bulbar/retinal telangiectasia easily clinch the diagnosis of A-T. Serum alpha-fetoprotein (AFP) level should be done. Progressive ataxia usually develops after 5 years.[2] Treatment of A-T is mainly symptomatic and supportive. The cornerstone treatment for the associated immunodeficiency is by regular intravenous immunoglobulins (IVIGs) and appropriate antibiotics for the repeated sinopulmonary infections. Nutritional support is required. There is no treatment for the progressive neuro-degeneration.[1] A-T is caused by mutations in ataxia telangiectasia mutated (ATM) gene, which encodes a protein kinase that has a major role in the cellular response to DNA damage. ATM gene is located on human chromosome 11 (11q22.3) and is composed of 69 exons spread across 150 kb of genomes.[3]

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CASE REPORT

A 4-year girl, presented to our hospital with severe bronchopneumonia and was started on parenteral broad spectrum antibiotics. She was the only child to consanguineous parents. The next day, she developed left sided pleural effusion followed by left-sided pneumothorax with increasing respiratory distress. She was shifted to pediatric ICU (PICU) where left intercostal drainage tube (ICDT) was inserted. CT chest was done and showed left lower lobe necrotising pneumonic consolidation, associated with bronchopleural fistula and large lobulated left pneumothorax (Figure 1). Pleural fluid culture was positive for both streptococcus mitis and candida albicans. Her peripheral blood smear showed picture of lymphopenia. Serum Immunoglobulin levels showed low IgA, low IgG, normal IgM and normal IgE. Whole exome sequencing (WES) study was done in Bioscientia Institute for Medical Diagnostics GmbH Centre for Human Genetics, Germany, confirming the diagnosis of A-T with a novel genetic variant. She received IVIG along with proper IV antibiotics and antifungal medications. Follow-up CT chest showed significant improvement. MRI brain showed mild cerebellar degeneration as shown in Figure 2. Her serum AFP was significantly high. During her follow-up in the clinic, she was noticed to have mild ataxia, but her conjunctivae continued to be clear.

DISCUSSION

Community acquired pneumonia (CAP) in children may be complicated with necrotising pneumonia (NP) in both immuno-

comptent and immunodeficient patients.[4] The main pathogens for NP in children are streptococcus pneumoniae and staphylococcus aureus.[4]

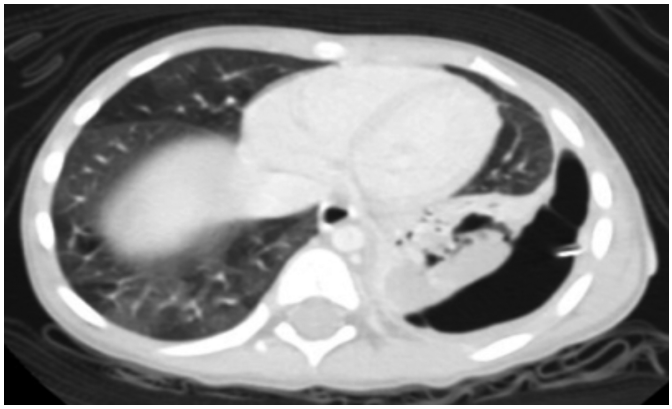

Figure1: CT chest showing lobulated left pneumothorax.

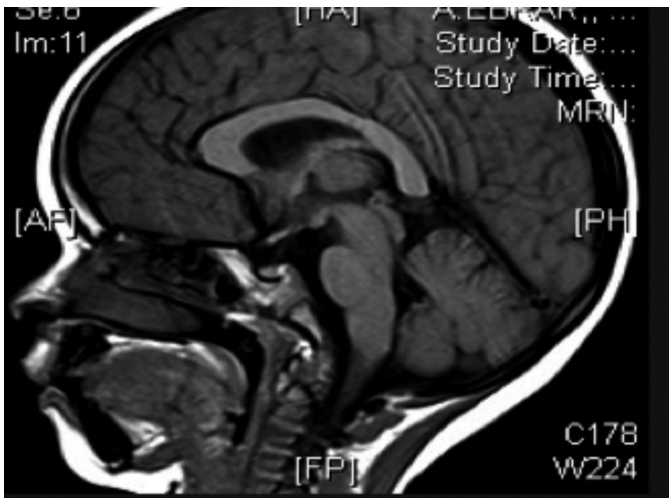

Figure2: MRI brain with cerebellar degeneration.

As our patient had severe complicated necrotising pneumonia, we started to investigate for expected underlying immunodeficiency. There was history of delayed walking and delayed speech, which could be an early non-specific manifestation of A-T. Our patient had lymphopenia and low levels of both IgG and IgA. Most of the patients with A-T have different abnormalities of their immune system.[5] The most reported abnormalities in A-T patients are significantly low levels of one or more classes of immunoglobulins (IgG, IgA, IgM or IgG subclasses)and lymphopenia, especially affecting T-lymphocytes.[6] Most of the people with A-T will have significantly higher levels of serum AFP, which increases with time.[2] MRI brain showed mild cerebellar degeneration; however, neuroimaging studies in early childhood could be normal in most A-T patients.[7] Our patient was 4 years old and did not have telangiectasia; but this does not exclude the diagnosis of A-T, as telangiectasia usually will occur later by the age of 5–8 years or may not occur. A-T is an autosomal disorder caused by mutations in the ATM gene.[1] We performed WES study for our patien in Bioscientia Institute for Medical Diagnostics GmbH Centre for Human Genetics, Germany. We detected a novel genetic variant of A-T, which is homozygous 1-bp duplication c.5172dupA p. (Asp1725Argfs*24) (chr11:108170607dup: hg19) in exon 34 of the ATM gene. This novel genetic variant was reported by all bioinformatic analysis tools used by Bioscientia Institute for Medical Diagnostics GmbH Centre for Human Genetics, Germany to be pathogenic. Our patient had clinical (severe pulmonary infections, ataxia) and laboratory picture of A-T (lymphopenia, low immunoglobulins IgA and IgG, and high level of AFP) along with cerebellar degeneration detected by MRI brain and this pathogenic mutation in ATM gene, so diagnosis of A-T was confirmed.

To the best of our knowledge, this variant has never been described in the literature, nor been annotated in genetic databases so far. There are more than 500 mutations in ATM gene reported uptill now, related to the development of A-T. In 2017, Mortaz *et al.* reported a new A-T mutation in an 11-year female.[8]

We highly recommend that any child with severe complicated NP should be investigated for underlying immunodeficiency. Early identification and management of underlying immunodeficiency will carry better prognosis and better quality of life for those suffering from this disease. NP complicated with bronchopleural fistulae in A-T patients can be treated successfully with proper antimicrobials and IVIGs without surgical intervention.

PATIENT'S CONSENT:

Informed consent was obtained from the parents of the patient to publish the data concerning this case.

CONFLICT OF INTEREST:

There is no conflict of interest among the authors.

AUTHORS' CONTRIBUTION:

WNA: Responsible about writing the case.
SAA: Approved the whole exome sequencing test and its results.
MAS: Pediatric intensivist, treated the patient in PICU.
ASA: Pediatric infectious disease consultant, responsible about the patient.
MFI, WFM: General paediatrics primary treating team responsible about treating and following up the case.
WFM: Supervisor consultant, helped and guided the first author in writing the case report.
All the authors reviewed and agreed about the submitted case report.

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