CASE REPORT
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Ataxia Telangiectasia: A Case Series from a Consanguineous Marriage

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ABSTRACT

Ataxia Telangiectasia (AT) is a rare autosomal recessive disease with features of progressive cerebellar atrophy, immunodeficiency, and enhanced cancer susceptibility due to mutations in the ataxia telangiectasia mutated (*ATM*) gene. However, despite evidence from patients with AT in consanguineous Iranian families, limited information is still available on the genotype-phenotype association. This paper presents a familial case series of AT in Yazd, Iran, with a novel homozygous *ATM* mutation.

This report examines a consanguine family in Yazd, Iran, with four members presenting with symptoms characteristic of AT, including progressive neurological decline, cerebellar atrophy, immunodeficiency, elevated alpha-fetoprotein, and recurrent infections.

Genetic analysis confirmed a novel homozygous mutation of the *ATM* gene (c.1834C>A; p.Leu612Ile), which is a non-conservative substitution. It is predicted to result in loss of function, and parents were carriers of the mutation. Treatment included intravenous immunoglobulin, prophylactic antibiotics, and supportive care. One of the patients died due to severe infection despite intervention.

This case series highlights the impact of consanguinity on the occurrence of AT and the supporting role of genetic testing in diagnosing *ATM* mutations. The results emphasize the need for improved genetic counseling, family planning, early immunological therapy, and culturally tailored public health strategies to effectively manage AT in consanguineous populations.

Keywords: Ataxia telangiectasia; Ataxia telengiectasia mutated gene; Consanguinity; Immunodeficiency

INTRODUCTION

Ataxia Telangiectasia (AT) is a rare, autosomal recessive neurodegenerative disorder caused by ataxia telengiectasia mutated (*ATM*) gene on chromosome 11q22–23. This disorder involves defective DNA repair, cerebellar ataxia, telangiectasia, immunodeficiency, predisposition to cancer, and decreased lifespan.[1,2] Ataxia Telangiectasia affects approximately 1 in 40 000–100 000 live births worldwide, though incidence may be higher for specific populations. AT is due to a mutation in the *ATM* gene and includes a report of 1400 mutations, leading to neurodegeneration, immunodeficiency, and an increased risk of cancer via loss of function of protein encoded by *ATM* gene in maintaining genomic stability.[3,4,5]

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Genetic diagnosis is crucial for identification, genetic counseling, and management.[6] Despite limited regional data, a study on 43 Iranian AT patients reported diverse clinical features, including ataxia (100%), telangiectasia (83%), infections (70%), and hepatosplenomegaly (12%). Among those with severe disease, telangiectasia, immune defects, and recurrent infections were particularly prominent. Genetic analysis identified 34 distinct *AT* mutations, including 9 novel mutations, nonsense (27%) and large deletions (23%) as most common. Null mutations (nonsense/frameshift) significantly increased risk of 7.3-fold for severe phenotypes, highlighting the genotype-phenotype correlations and the clinical importance of genetic profiling in Iranian AT patients.[7]

This case study describes and discusses a pattern of AT within a consanguineous family in the city of Yazd, Iran. The present study aims to provide valuable clinical and laboratory insights into AT in the scenario of a consanguinity within an Iranian family.

METHODS

This case series reviewed multiple patients from a consanguineous family in Yazd, Iran with suspected ataxia telangiectasia. The diagnosis was based on clinical presentation, high serum alpha-fetoprotein levels, and genetic testing. Further assessments included immunological studies, MRI of the brain, and whole exome sequencing followed by Sanger sequencing. Variant pathogenicity was assessed using American College of Medical Genetics and Genomics criteria.

RESULTS

Patients

The patients showed classic signs of progressive cerebellar ataxia and oculocutaneous telangiectasias that typically presented in early childhood. Ocular telangiectasias were quite prominent, especially in the bulbar conjunctiva. The cerebellar atrophy, particularly the vermis, and moderate atrophy affecting the brainstem were the most prominent neurological manifestations. cutaneous vascular changes with dilated vessels were evident on the face, neck, and ears. In the patients' neurological presentation, there was progressive cerebellar ataxia, hypotonia, oculomotor apraxia (abnormal eye movement coordination), dysarthria (difficulty in speech articulation), and developmental delay. The Patients also presented with recurrent sinopulmonary infections such as pneumonia and chronic sinusitis, often with the underlying component of immunodeficiency.

Case 1

The first patient was a 12-year-old girl born to consanguineous parents. She was unable to sit independently and could not maintain head control from 9 months of age by age of 2 years, she developed recurrent episodes of respiratory infection and otitis media. Ocular telangiectasias were apparent at age 3 years. Although she could walk initially, this ability deteriorated over time: she walked until age 7, after which gait gradually worsened and she developed frequent falls; by age 8. At age 5 years, she was diagnosed with AT. She also suffered CMV-associated pulmonary and ocular infections. Unfortunately, she passed away at 12 years of age due to severe infections.

Case 2

The second patient is the younger sister of the first and currently 10 years old. She exhibits neurological deficits and recurrent infections. Sitting imbalance was evident from 8 months of age. Genetic testing confirmed AT at age 4. She developed ocular telangiectasias at the same age (Figure 1). Despite neurological deficits and recurrent infections, she continues to receive care under the AT-specific treatment protocol.

Figure 1. Bulbar conjunctiva telangiectasia in case 2 (a 10-year-old girl).

Case 3

The third patient is a 14-year-old girl who is the daughter of the maternal uncle of the two previous patients, resulting from a consanguineous marriage. She also suffered from walking difficulties from age 2 years. Over time, she developed recurrent falls, involuntary eye and head movements at rest. Recurrent sinus and ear infections have been a significant challenge in her clinical course. She had severe neurological disorders and has been treated as the AT-specific treatment protocol.

Case 4

The fourth case is a 13-year-old boy who is a first cousin of the first patient, resulting of a consanguineous marriage. His onset of symptoms occurred between ages 4 and 5 years, beginning with walking difficulty and recurrent falls. He developed ocular telangiectasias and has suffered from recurrent respiratory infections, otitis media, and sinusitis. Despite neurological complications and frequent infections, he remains clinically stable. His treatment is also similar to that of the other affected family members. He also exhibits Bulbar Conjunctiva Telangiectasia. His brain magnetic resonance imaging (MRI) demonstrated cerebellar, particularly involvement of the vermis and moderate brainstem (Figure 2). All patients were clinically diagnosed with AT based on clinical examination, symptoms, and supporting diagnostic tests (increased serum alpha-fetoprotein levels), and were confirmed by genetic testing.

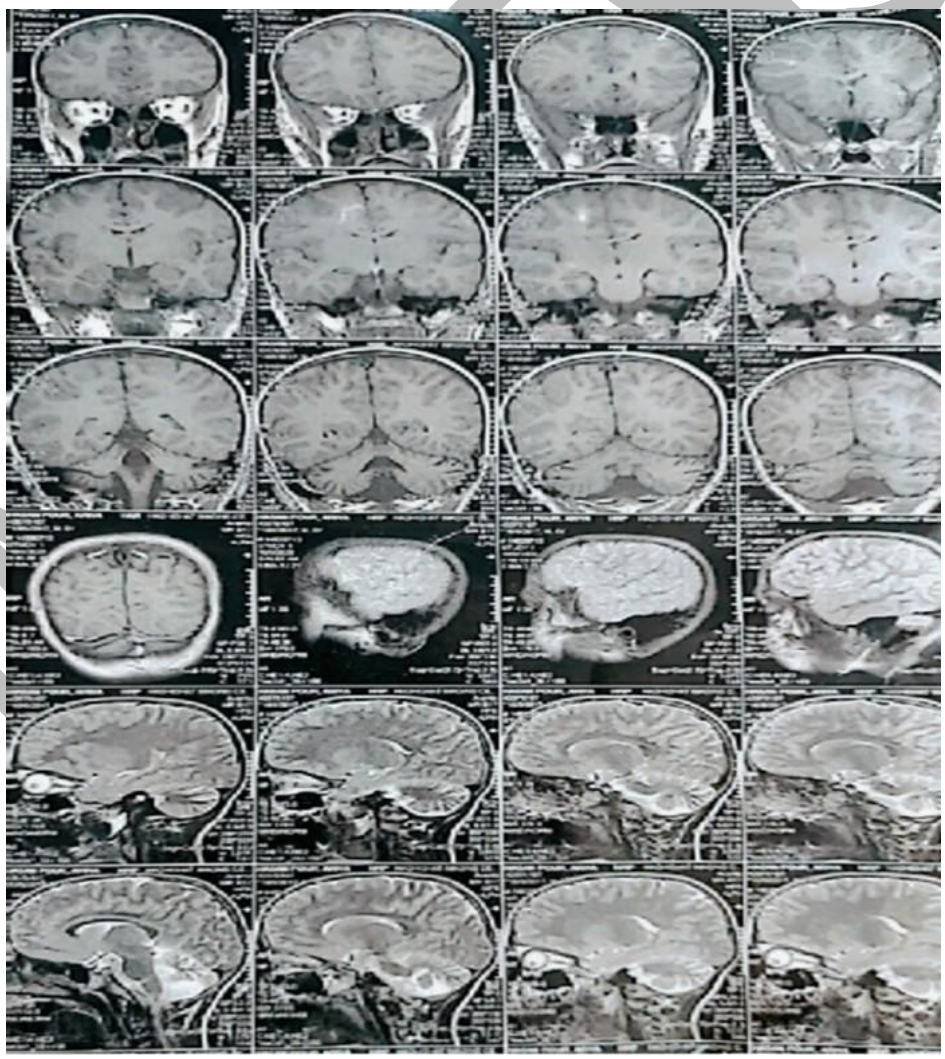

Figure 2. Brain MRI in case 4 (a 13-year-old boy), presenting atrophy of the cerebellum, particularly the vermis and moderate atrophy of the brainstem.

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Family Pedigree Analysis

The family pedigree tree (Figure 3) exhibits a pattern of consanguineous marriages, which shows the autosomal recessive Ataxia Telangiectasia. AT emerged in the third generation, affecting four affected individuals. The unaffected parents in generation II are likely carriers of a pathogenic variant of *ATM* gene, consistent with an autosomal recessive inheritance pattern.

Genetic Analysis

Whole exome sequencing identified a novel homozygous mutation in the *ATM* gene (NM_000051.4: c.1834C>A, exon 12) in the affected siblings, whereas both parents were heterozygous carriers. Figure 4 depicts the results of sanger sequencing for case 1 and 2. The homozygous mutation c.1834C>A resulted in an amino acid substitution (p.Leu612Ile), which is a non-conservative substitution where leucine is replaced with isoleucine, affecting protein function. This mutation has been submitted to ClinVar with the variation ID 2818378 and this variant is currently classified as uncertain significance due to limitations of evidence demonstrating pathogenicity. However, based on its non-conservative substitution, its novelty, potential disruptive effect on the function of protein encoded by *ATM* gene, along with its association to the clinical presentation of our patients, this variant could be classified as likely pathogenic in consideration of the American College of Medical Genetics criteria, pending additional functional validation.

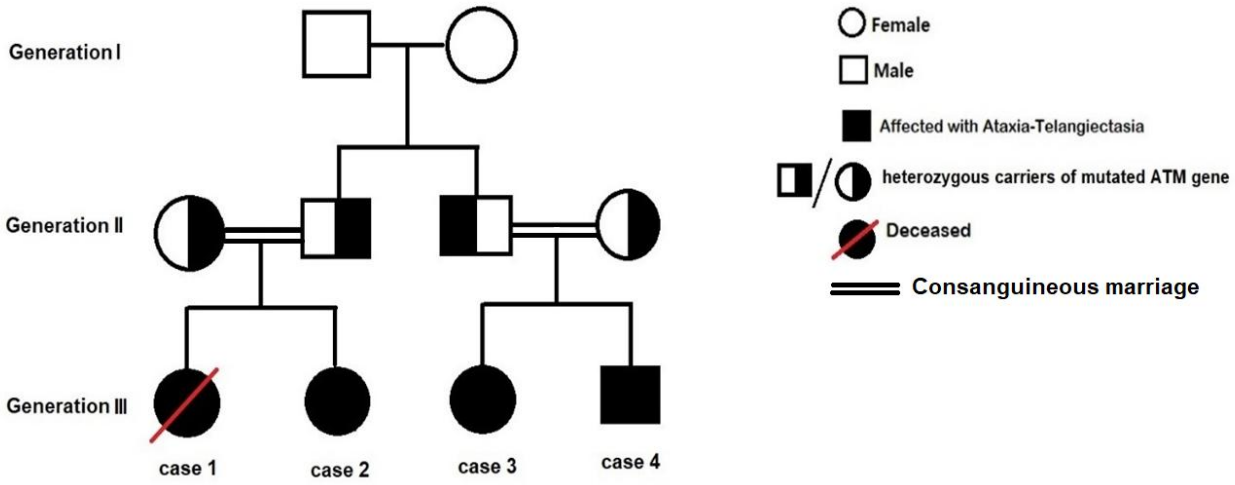

Figure 3. The family pedigree showing autosomal recessive inheritance of Ataxia Telangiectasia in a consanguineous Iranian family. The first patient was a girl born from a consanguineous marriage (cousin union),. Her parents (second generation) appear healthy but are carriers of the faulty gene. The second patient was the younger sister of the first patient. The third patient was the female cousin of the first two patients; her father was the uncle of the first and second patients. She was also the child of a cousin marriage. The fourth patient was boy who was also the male cousin of the first two patients. Their parents are also carriers of the same gene.

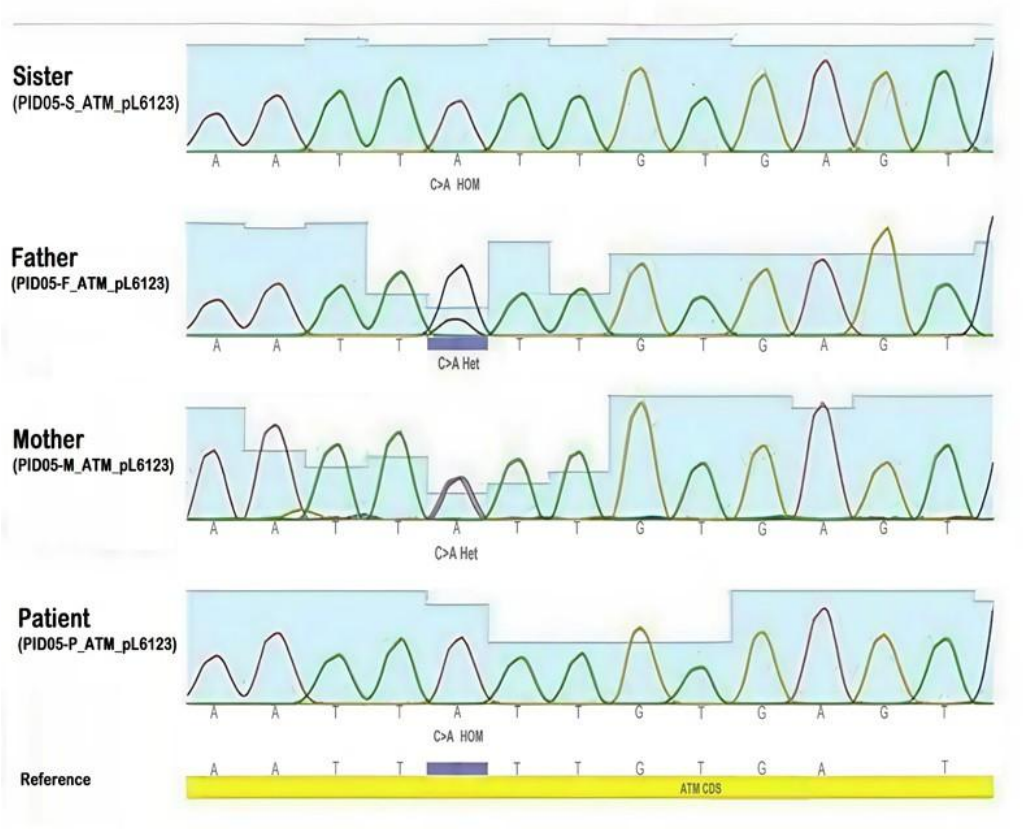

Figure 4. Sanger sequencing validation of the *ATM* mutations in family members. C>A Hom: C>A homozygous mutation; C>A Het: C>A heterozygous mutation; *ATM* CDS: coding sequence of the *ATM* gene.

Laboratory Findings

Laboratory data from all AT cases showed that CD3 (T cells) percentages were within normal pediatric range (62.8–68.3%; mean 64.65%). CD4 (Helper T cells) percentages ranged from 34.2–44.2%, were also normal, with Case 4 showing the highest value (44.2%), suggesting relatively better helper T cell immunity. CD8 (Cytotoxic T cells) levels were normal across cases (28.4–33%), with case 1 showing the lowest (28.4%) and case 4 showing the highest (33%). Normal levels of CD8 T cells indicated a preserved cellular immunity. The CD16/CD56 (NK Cells) percentages in all cases (11.2–13%) within the normal range. However, B cell (CD19) percentages in case 1 (9.7%), case 2 (9.5%) and case 3 (9.8%) were below the pediatric reference range, indicating B-cell lymphopenia. But it was in the normal range for case 4 (11.5%). HLA-DR expression was found to be low in all cases; however, this finding alone cannot be interpreted as impaired antigen presentation without further phenotyping of antigen-presenting cells and additional flow cytometry metrics such as mean fluorescence intensity and gating strategy used. IgA, IgM, and IgG levels were all significantly below their respective reference ranges, indicating severe hypogammaglobulinemia. IgE remained relatively low but normal range compared to the upper reference limit, which is consistent with AT-related immunodeficiency. Immunological evaluation revealed very low diphtheria and tetanus antibody levels (<0.2 IU/mL), indicating poor vaccine response, consistent with immunodeficiency aspect of AT. Alpha-fetoprotein (AFP) levels were elevated in all cases, supporting AT diagnosis. Additionally, positive Direct Coombs tests in two cases revealed the presence of non-specific cold and warm autoantibodies, indicating autoimmune dysregulation (Table 1).

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Table 1. Laboratory findings in four cases.

Laboratory data	Test	Case 1	Case 2	Case 3	Case 4	Mean ± SD	IQR ranges	Reference Range
Flow Cytometry	CD3, %	62.8	63.5	64	68.3	64.65 ± 2.15	63.15_66.15	Adults: 60–85, Children: 61–82
	CD4, %	34.2	36.7	35.4	44.2	37.63 ± 3.90	34.8_40.45	Adults: 30–65, Children: 30–54
	CD8, %	28.4	31.8	32.6	33	31.45 ± 1.81	30.1_32.8	Adults: 14–38, Children: 16–37
	CD16/CD56 (NK Cells), %	12.2	11.2	11.7	13	12.02 ± 0.66	11.45_12.6	Adults: 6–24, Children: 4–14
	CD19 (B Cells), %	9.7	9.5	9.8	11.5	10.13 ± 0.80	9.6_10.65	Adults: 3–18, Children: 10–38
	HLA-DR (Flow Cytometry)	Low	Low	Low	Low	Low	_	Adults ~ 10 000–30 000 Infants ~ 5000 to 15 000 Children (> 1 year) ~ 10 000 to 25 000
Serology	IgA mg/dL (Nephelometry)	<9	<14	<15	<23	15.25 ± 5.02	11.5_19	86–320
	IgM mg/dL (Nephelometry)	<16	<16	<18	<21	17.75 ± 2.05	16_19.5	35–255
	IgG mg/dL (Nephelometry)	<204	<248	<255	<267	243.5 ± 23.80	226_261	656–1351
	Serum IgE, IU/mL	23	36	44	58	40.25 ± 12.70	29.5_51	Adults: Up to 200, 3–16 Years: Up to 280
Immunology	Diphtheria Ab, IU/mL	0.1	0.1	0.1	0.2	0.125 ± 0.043	0.1_0.15	>1.0 Immune, 0.1–1.0 Booster Recommended
	Tetanus Ab, IU/mL	0.1	0.1	0.1	0.2	0.125 ± 0.043	0.1_0.15	>1.0 Immune, 0.1–1.0 Booster Recommended

Table 1. Continued...

Laboratory data	Test	Case 1	Case 2	Case 3	Case 4	Mean ± SD	IQR ranges	Reference Range
Alpha-Fetoprotein	AFP, ng/mL	97.0	85	95	77	88.5 ± 8.05	81_96	Up to 50
Immunohematology	Direct Coombs Test (DCT)	Positive	Positive	Negative	Negative	_	_	Negative
	Antibody Type	Non-specific cold and warm autoantibodies	Non-specific cold and warm autoantibodies	Negative	Negative	_	_	-
	Auto Control Test	Positive (1+)	Positive (1+)	Negative	Negative	_	_	Negative

Flow Cytometry measured the level of HLA-DR protein expression on the surface of immune cells. "Low" means reduced expression of HLA-DR protein. AFP: alpha-fetoprotein; CD: cluster of differentiation; DCT: Direct Coombs Test; HLA-DR: human leukocyte antigen – DR isotype; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IQR: interquartile ranges; NK: natural killer; SD: standard deviation.

Management and Outcomes

All patients received prophylactic antibiotics and intravenous immunoglobulin (IVIG) therapy according to the European Society for Immunodeficiencies (ESID) guidelines to manage recurrent infections and severe immunoglobulin deficiencies. Supportive care including Vitamin E and physical therapies (coordination exercises) was given to manage progressive neurological deterioration and complications of autoimmunity. The IVIG was administered at a dose of 400–600 mg/kg every 3–4 weeks until IgG levels and clinical status normalize. Eventually, despite medical intervention, one of the patients died due to severe infections.

DISCUSSION

This study describes Ataxia Telangiectasia in a consanguineous family from Yazd, Iran; four children were diagnosed with AT due to a novel homozygous *ATM* gene mutation (c.1834C>A; p.Leu612Ile), involving a non-conservative substitution predicting to disrupt protein function. Clinically, they demonstrated progressive neurological degeneration with cerebellar atrophy, recurrent infections, serious immune deficiencies, and elevated AFP. Immunological testing reaffirmed B-cell lymphopenia, severe hypogammaglobulinemia, very low diphtheria and tetanus antibody levels, decreased HLA-DR expression, and positive Direct Coombs tests, indicating profound immunodeficiency and possibly autoimmune dysregulation. Altogether, this evidence exemplifies the multifaceted immune impairment of AT. The absence of symptoms in the earlier generations can be due to the autosomal recessive inheritance pattern of Ataxia Telangiectasia.

Our findings supported the reports of Badalzadeh et al on their Iranian cohort. [5] Their study focused on clinical characterization and mutation analysis of unrelated families while our case series has further highlighted familial clustering in consanguineous families, and reported the consanguinity as a key factor in autosomal recessive inheritance.

Kamat (2023) described a rare case of AT, with classic neurological symptoms and elevated AFP,[8] with similar clinical features to our cases Brain MRI indicated cerebellar atrophy, which coincided with Kamat's findings. Unlike Kamat's sporadic case in India, our findings reveal a more profound familial clustering due to high rates of consanguineous marriages in Iran.

Mahdieh et al provided pathogenic variants in 42 genes among 162 Iranian patients with cerebellar ataxia from diverse regions, achieving a genetic diagnostic rate of 59.9% and a significant prevalence of variants in *PLA2G6*, *ATM*, *SACS*, and *SCA* genes.[9] Our findings are consistent with earlier reports (Mahdieh et al., 2024) showing that consanguinity increases the risk of developing early-onset autosomal recessive ataxias in Iranian families. Similarly, other studies also indicated a high prevalence of AT related to consanguineous families, emphasizing the impact of endogamy on AT prevalence.[10-12] In contrast, Shao et al described a Chinese patient with a novel heterozygous *ATM* variant, highlighting the diverse genetic spectrum of AT.[13] While consanguinity is a significant risk factor in regions like Iran, de novo or compound heterozygous mutations in non-consanguineous populations underscores the need for culturally tailored public health strategies.

Immunodeficiency was a hallmark feature in our cases, which was similar to those reported by previous studies.[10-13] The immunological findings across these studies highlight the critical role of early immunological assessments and prophylactic treatments to prevent severe infections in AT patients. Our treatment strategies, including prophylactic antibiotics and IVIG, were consistent with the approaches described by Mahadevappa et al and Al-Muhaizeaet et al's studies.[10,11] Despite similar management, AT has a poor prognosis due to its progressive and multifaceted nature. Mahadevappa et al reported high rate of mortality, mainly because of infections and malignancies.[10] Although elevated AFP levels were consistent with a diagnosis of AT in all patients, elevated AFP may also correlate with liver dysfunction or malignancies. However, in this study, hepatic panels were normal, and malignancy evaluations (i.e., imaging, tumor markers, etc.) were not performed, thus elevated AFP levels were predominantly interpreted as consistent with AT. So, further investigation of malignancy risk should be performed in future studies.

The lack of detailed hematologic evaluation and phenotyping of antigen-presenting cells are limitations of the study.

This study shows that how a rare genetic disease might dramatically alter the course of a common condition inside a generation. Also, it underlines the

need of more investigation on AT's genetic diversity, new treatments, and public health policies to increase awareness about consanguinity hazards, support genetic counseling, and lower genetic disorders in vulnerable populations.

STATEMENT OF ETHICS

Ethical approval was exempted for this case report, which includes a literature review. Informed consent was obtained from the patient's parents for this case report.

FUNDING

The authors report no internal or external funding for this paper.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The findings of this study are available author upon reasonable request from the corresponding by email.

AI ASSISTANCE DISCLOSURE

Not applicable.

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