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CASE REPORT

Treatment-related toxicities in acute lymphoblastic leukemia in a child with Marfan syndrome

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ABSTRACT

Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in the fibrillin-1 gene. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. The coexistence of MFS and ALL is rare and presents a unique clinical challenge. We report the case of an 8.5-year-old boy with MFS who developed precursor B-cell acute lymphoblastic leukemia with the ETV6-RUNX1 fusion gene. He achieved complete remission with initial chemotherapy. Two years later, he experienced a relapse involving the testes and central nervous system. Subsequent treatment led to severe complications. Whole exome sequencing revealed multiple pathogenic variants, including a CHEK2 mutation, potentially contributing to the malignancy and treatment-related toxicities. This case highlights the potential role of dysregulated transforming growth factor β signaling in MFS contributing to leukemogenesis. The patient's severe complications and co-occurrence of MFS underscore the need for personalized therapeutic strategies and comprehensive, multidisciplinary care. Further research is essential to improve clinical outcomes.

KEY WORDS:
complications, relapse, WES, acute lymphoblastic leukemia, Marfan syndrome.

INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant disorder affecting connective tissue, particularly influencing the skeletal, ocular, and cardiovascular systems. It is caused by mutations in the pleiotropic gene encoding the glycoprotein *fibrillin-1* (*FBN1*), a crucial protein for connective tissue integrity. It occurs in approximately 1 in 5000 individuals worldwide, affecting all ethnic groups equally, with both genders affected with the same frequency [1]. The disease is characterized by variable penetrance and expression across individuals and families. In classical cases, individuals with MFS exhibit tall stature (dolichostenomelia), elongated limbs, slender fingers (arachnodactyly), underdeveloped adipose tissue, and lens dislocation (ectopia lentis). Additional features include characteristic changes in the musculoskeletal system such as elongated tubular bones, hypermobility of joints, dilation of the aorta, an increased risk of aortic aneurysms and acute aortic dissections [1]. About 25% of MFS cases are due to de novo mutations, with occasional gonadal mosaicism allowing unaffected parents to pass the mutation to their children. Various mutations in *FBN1* lead to decreased *FBN1* levels, affecting the structure and function of connective tissues [1].

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. It arises from the uncontrolled proliferation of lymphoid cells, mainly pre-B-cells

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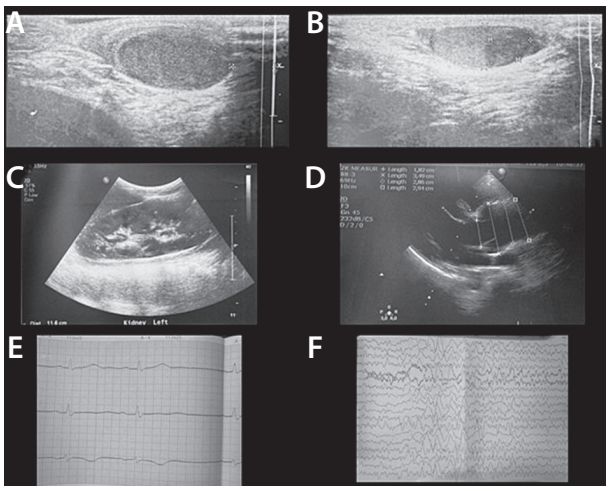

FIGURE 1. A) Left testis before surgical removal. **B**) Right testis with visible leukemic infiltration. **C**) Double collecting system of the left kidney. **D**) Enlargement of the aortic root and ascending aorta typical for Marfan syndrome. **E**) Electrocardiography recording in leads I, II, III showing slow electrical activity and right bundle branch block. **F**) Electroencephalography recording with spike-wave complexes

(80–85%), and less frequently T-cells (10–15%) and mature B-cells (< 5%). Precursor B-cell acute lymphoblastic leukemia (pre-B-ALL) represents the majority of ALL cases, involving over 20 subtypes influenced by genetic alterations such as chromosomal aneuploidy, gene rearrangements, and point mutations [2, 3]. These mutations disrupt various cellular pathways, including lymphoid development and cell cycle regulation. Whole exome sequencing (WES) has become a new tool in identifying these mutations by analyzing the protein-coding regions of the genome [4, 5].

Recent therapeutic protocols increasingly emphasize a personalized approach to patient management, considering individual variability in genetics, environment, and lifestyle factors to optimize treatment outcomes.

This case report describes an 8.5-year-old boy diagnosed with MFS and pre-B-ALL, attributed to a complex interplay of multiple genetic mutations. It underscores a particularly challenging medical scenario arising from the convergence of a genetic disorder, an acquired malignancy, and severe chemotherapy complications in a pediatric patient.

CASE REPORT

An 8.5-year-old patient (with a prior diagnosis of MFS), who presented with high fever, weight loss and limb pain was diagnosed with pre-B-ALL. In clinical examination the boy was in quite good general condition, marfanoid body build, no enlarged lymph nodes or splenomegaly. Initial white blood cell (WBC) count was 17,000/mm^3, bone marrow morphology was consistent with ALL. Immunophenotype revealed CD79a+/TdT+/CD34+/CD19+/CD22+/CD10+/CD20-/cIgM-/κ-/λ-/CD13+, which corresponded to common ALL with co-expression of CD13 and partial co-expression of CD33. Fluorescence *in situ* hybridization (FISH) showed an *ETV6*/*RUNX1* fusion in blastic cells. The patient was stratified to an intermediate risk group and was treated with the Acute Lymphoblastic Leukemia Berlin-Frankfurt-Münster 2009 protocol. After induction he obtained complete remission. Treatment complications included coagulation abnormalities after L-Asparaginase administration and prolonged pancytopenias requiring supportive therapy with granulocyte colony-stimulating factor (G-CSF) and causing prolongation of maintenance.

Two years post-diagnosis, the patient was readmitted due to combined testicular and central nervous system relapse. The central nervous system symptoms included a persistent headache lasting for a week and gait disturbances detected at neurological examination. Ultrasound showed an enlarged left testis (22 × 11 mm) and a hypoechogenic area in the right testis, with increased vascularization indicating disease infiltration (Figure 1). The left testis was surgically removed, revealing infiltration of B-cell line lymphoblastic leukemia/lymphoma infiltration.

The patient experienced severe therapy complications including polyneuropathy diagnosed as likely toxic multifocal axonal-demyelinating neuropathy and osteoporosis with Th7-Th8 vertebrae height reduction. Magnetic resonance imaging (MRI) of the lumbar spine detected Th12-S3 edema suggestive of myopathy. Additional complications included periodic bradycardia (around 40 beats per minute), mild cerebral edema without neurological deficits or significant pathology, mucositis, coagulation disorders, elevation in liver function tests, and pancytopenia. Lung MRI showed several millimetric nodular changes in both lungs and a slightly larger infiltrative change in the left lung hilum. Computed tomography (CT) confirmed single nodules in both lungs and areas resembling "ground glass," likely of fungal origin. The boy presented with fevers; the observed changes improved on antifungal empiric treatment.

The patient was also diagnosed with a double renal collecting system on the left side by ultrasonography of the retroperitoneal space and abdominal CT scan. Echocardiogram revealed an enlarged aortic root (Z-score +3.9) and ascending aorta. Chest X-ray revealed the elongated aorta, extending to the sternoclavicular joints. An electrocardiography (ECG) indicated a first-degree atrioventricular block and a pronounced right bundle branch block (Figure 1 E). An ophthalmological examination indicated hypermetropia requiring corrective glasses. Throughout the year, the patient underwent multiple hospitalizations, required multidisciplinary care and repeated blood cell transfusions. Neurophysiological signs of multifocal motor neuropathy with axonal-demyelinating characteristics were observed: severe back pain syndrome with subsequent weakening of muscle strength, features of polyneuropathy (gait disturbance, numbness

TABLE 1. Overview of complications observed in the presented patient with Marfan syndrome and acute lymphoblastic leukemia with common terminology criteria for adverse events – toxicity grading standards [6]

System	CTCAE term	CTCAE grade (G1–G5)
Neurological	Peripheral motor neuropathy	[G3]
Neurological	Seizure (epilepsy – EEG confirmed)	[G2]
Neurological	Peripheral sensory neuropathy	[G2]
Musculoskeletal	Osteoporosis (spine Th7-Th8)	[G3]
Musculoskeletal	Musculoskeletal and connective tissue disorder	[G2]
Hematological	Anemia, neutrophil count decreased, platelet count decreased	[G3]/[G4]/[G4]
Cardiovascular	Bradycardia (sinus bradycardia)	[G1]
Cardiovascular	Atrioventricular block first degree, conduction disorder (bundle branch block)	[G1]/[G1]
Digestive	Stomatitis (oral mucositis)	[G1]
Infectious	Abscess (musculoskeletal)	[G3]
Infectious	Oral infection – fungal	[G1]
Infectious	Pneumonia	[G3]
Immune system	Immunoglobulins decreased (pan-hypogammaglobulinemia across IgG/IgA/IgM)	[G2]

CTCAE – common terminology criteria for adverse events, EEG – electroencephalography, Th – thoracic vertebra

in the area of the fifth and fourth fingers of both hands, overall significant weakness in the upper and lower limbs, significant weakening of tendon reflexes in the limbs, very small range of active movements, disturbances in the functioning of the rectal sphincter). Muscular atrophy, especially in the distal parts of the limbs, was noted, along with decreased muscle tone and tendon reflexes. The initial suspicion of Guillain-Barré Syndrome was modified to a diagnosis of sensory-motor polyneuropathy. He required intensive physiotherapy. The recommendation to avoid neurotoxic therapy was established. Vincristine and vindesine were replaced with etoposide. Despite this, the patient experienced seizures leading to an epilepsy diagnosis, managed with clonazepam and permanent phenobarbital as prophylactic treatment. Episodes of seizures were confirmed by electroencephalography (Figure 1 F). Further antiseizure treatment modification was required. An MRI of the lumbar and sacral region revealed an inflammatory infiltrate with abscess formation, which was treated with antibiotics. Observed complications are summarized in Table 1.

The patient has been followed in a dedicated late-effects clinic and required a multi-specialist team for MFS, cardiac problems, epilepsy, secondary immunodeficiency, intestinal bacterial overgrowth, trachoma, visual impairment and alopecia. Regarding the cardiac domain, surveillance performed as part of routine cardio-oncology follow-up documented stable aortic root dilatation and conduction abnormalities (first-degree atrioventricular block and right bundle branch block) with intermittent sinus bradycardia. Extended ambulatory monitoring (24 h Holter ECG) confirmed these findings without additional clinically significant arrhythmias and did not alter management. The patient remained asymptomatic from the cardiac standpoint – no chest pain, syncope, cyanosis, or heart-failure signs – and therefore did not receive antiarrhythmic medications. Ongoing management consists of periodic echocardiography and ECG/ambulatory monitoring, with cardiology oversight coordinated within survivorship care.

Regarding secondary immunodeficiency, serial immunology demonstrated reductions below age-adjusted lower limits across all immunoglobulin classes (IgG, IgA, and IgM), consistent with chemotherapy-induced hypogammaglobulinemia. The patient continues to receive scheduled intravenous immunoglobulin replacement with good tolerance. The major infectious events describes above an inpatient-treated pneumonia with imaging features compatible with fungal etiology and a musculoskeletal abscess which occurred during documented neutropenia and protocol-mandated corticosteroid exposure, and were interpreted as complications of therapy-induced immunosuppression superimposed on antibody deficiency.

Taking into account coexisting ALL and MFS, WES was performed in the patient. It revealed numerous genetic abnormalities potentially associated with both the patient's malignancy and the various complications experienced during treatment. Table 2 presents potentially significant genetic variants that could predispose the patient to therapy complications, a spectrum of complications, the malignancy itself, and the identified gene variants suggest a potential link between clinical symptoms and genetic alterations that are not associated with MFS by itself.

The last follow-up visit took place in August 2025. The patient remains in a stable condition without clinical indications of relapse. Interval assessments have not revealed new abnormalities. Cardiovascular findings consistent with underlying MFS persist without progression, and the neurological status is likewise stable. Care focuses

TABLE 2. Key genetic mutations identified through whole exome sequencing

Gene ClinVar status, classification	Associated diseases	Inh.	Sequence change, impact on protein product, location	Variant parameters	Genotype, variant identifier	ACMGG classification
CHEK2, 100.0% – N	Hereditary cancer-predisposing syndrome, familial breast cancer	AD	c.573+1G>A; strong impact: splicing mutation; AT = 18/24; APCT = 11/15; chr22: 28725242	ExAC = 0.00016; gnomAD-G = 0.00019; maxAF = 0.00049; maxPOP = FIN; SIFT = 0.008; PhastCons = 1; GERP = 4.860	Het. C/T; rs121908698	P
MYH7, 40.5% – SM	Myopathy, myosin storage, autosomal recessive scapuloperoneal myopathy, congenital myopathy with fiber type disproportion, hypertrophic cardiomyopathy 1, dilated cardiomyopathy 15, myosin storage myopathy, familial hypertrophic cardiomyopathy 1	AD, AR, H		SIFT = 0.008; PhastCons = 1; GERP = 5.550	Het. C/G; rs397516171	P
AP4B1, 39.0% – SM	Spastic paraplegia 47, autosomal recessive	AR	c.1160_1161delCA; p.Thr387fs; strong impact: frameshift mutation; AT = 3/14; APCT = 3/6; chr1: 113898754	ExAC = 0.00033; gnomAD-E = 0.00007; gnomAD-G = 0.00024; maxAF = 0.00071; maxPOP = ASJ; PhastCons = 0.999; GERP = 4.750	Het. CTG/C; rs587779388	P
ACO2, 33.1% – SM	Optic atrophy 9	AR	c.220C>G; p.Leu74Val; MIMM; AT = 2/7; APCT = 2/2; chr22: 41507837	ExAC = 0.00649; gnomAD-E= 0.00706; gnomAD-G = 0.00644; maxAF = 0.00706; maxPOP = NFE; SIFT = 0.009; PhastCons = 1; GERP = 2.540	Het. C/G; rs141772938	LP
LRP2, 36.0% – SM	Donnai-Barrow syndrome	AR	ENST00000263816.7; c.10202C>G; p.Thr3401Arg; MIMM; AT = 1/5; APCT = 1/2; chr2: 169177994	ExAC = 0.000003; gnomAD-E = 0.00007; gnomAD-G = 0.00003; maxAF = 0.00023; maxPOP = SAS; SIFT = 0.580; PhastCons = 1; GERP = 3.030	Het. G/C; rs200566335, rs20186953, c.2210C>T, p.Ser737Leu	VUS
FBN1, 100.0% – SM	Acromicric dysplasia, ectopia lentis, isolated ectopia lentis autosomal dominant, familial aortopathy, geleophysic dysplasia 2, MASS syndrome, Marfan lipodystrophy syndrome, MFS, stiff skin syndrome, thoracic aortic aneurysm	AD	ENST00000316623.9; c.510C>A; p.Tyr170*; strong impact: stop codon insertion; AT = 2/8; APCT = 1/2; chr15: 48596311	PhastCons = 0.772; GERP = –1.130	Het. G/A	VUS
ZNF423, 36.0% – SM	Nephronophthisis 14	AD, AR	ENST00000262383.6; c.3162C>G; p.His1054Gln; MIMM; AT = 7/8; APCT = 7/8; chr16: 46360326	SIFT = 0; PhastCons = 1; GERP = 4.150	Het. G/C	VUS

TABLE 2. Cont.

Gene ClinVar status, classification	Associated diseases	Inh.	Sequence change, impact on protein product, location	Variant parameters	Genotype, variant identifier	ACMGG classification
KCNQ1, 100.0% – N	Atrial fibrillation, familial atrial fibrillation 3, Beckwith-Wiedemann syndrome, hereditary deafness, Jervell and Lange-Nielsen syndrome 1, long QT syndrome 1, Romano-Ward syndrome, short QT syndrome 2, short QT syndrome	AD, AR, H	c.1511G>C; p.Asp504Ala; MIMM; AT = 1/9; APCT = 1/6; chr11: 2521545	SIFT = 0; PhastCons = 0; GERP = –3.410	Het. C/G	VUS
PTCH1, 100.0% – N	Basal cell carcinoma multiple, Gorlin syndrome, holoprosencephaly 7, holoprosencephaly sequence	AD, H	ENST00000428996.6; c.1159G>A; p.Gly387Arg; MIMM; AT = 9/27; APCT = 8/15; chr9: 97745680	gnomAD-G = 0; SIFT = 0; PhastCons = 1; GERP = 5.100	Het. C/T	VUS
WHSC1, 100.0% – N	4p partial monosomy syndrome	AD, SM	c.3599T>A; p.Leu1200Ile; MIMM; AT = 5/7; APCT = 5/7; chr4: 19067140	ExAC = 0.00001; gnomAD-G = 0.00001; maxAF = 0.00001; maxPOP = NFE; SIFT = 0.01; PhastCons = 0.014; GERP = 5.510	Het. T/A; rs72747720	VUS
NIPBL, 50.3% – SM	Cornelia de Lange syndrome 1, De Lange syndrome	AD, SM	c.7960G>A; p.Arg2654Gln; MIMM; AT = 2/8; APCT = 2/3; chr5: 37051815	ExAC = 0.00002; gnomAD-G = 0; gnomAD-E = 0.00001; maxAF = 0; maxPOP = NFE; SIFT = 0.007; PhastCons = 1; GERP = 5.690	Het. G/C; rs748438696	VUS
KIAA0556, 36.0% – SM	Joubert syndrome 26	AR	ENST00000618588.4; c.4522A>G; p.Asp1508Gly; MIMM; AT = 1/10; APCT = 1/3; chr16: 2777620	gnomAD-G = 0; SIFT = 0; PhastCons = 1; GERP = 4.750	Het. A/G	VUS
PCNT, 39.8% – SM	Microcephalic osteodysplastic primordial dwarfism type 2	AR	ENST00000359568.9; c.2524G>C; p.Glu842Gln; MIMM; AT = 1/8; APCT = 1/2; chr21: 46363849	SIFT = 0.049; PhastCons = 0.989; GERP = 3.520	Het. G/C	VUS
KCNJ10, 100.0% – N	Enlarged vestibular aqueduct syndrome, hereditary deafness, lesion ascending hearing loss and nonsyndromic deafness autosomal recessive, hearing loss and non-syndromic deafness, pendred syndrome, SeSAME syndrome	AR	c.1302C>T; p.Arg434Cys; MIMM; AT = 1/9; APCT = 1/8; chr1: 160041506	ExAC = 0.00002; gnomAD-E = 0.00007; gnomAD-G = 0.00001; maxAF = 0.00007; maxPOP = NFE; SIFT = 0.03; PhastCons = 0.747; GERP = 4.170	Het. C/T; rs575333314	VUS
RAD54L, 100.0% – N	Familial cancer of breast, malignant lymphoma non-Hodgkin, neoplasm of the breast	AD	ENST00000371975.8; c.466C>T; p.His156Tyr; MIMM; AT = 4/12; APCT = 4/8; chr1: 86456100	SIFT = 0; PhastCons = 1; GERP = 5.750	Het. C/T	VUS
MST1, 100.0% – N	Primary sclerosing cholangitis	AD	ENST00000404962.2; c.1793T>C; p.Val598Ala; MIMM; AT = 2/21; APCT = 2/3; chr3: 49846323	gnomAD-G = 0.00001; maxAF = 0.00001; maxPOP = NFE; SIFT = 0.002; PhastCons = 1; GERP = 5.460	Het. A/G	VUS

ACMGG – American College of Medical Genetics and Genomics, AD – autosomal dominant, APCT (allele percent) – the percentage of allele count from the total, AR – autosomal recessive, ASJ (Ashkenazi Jewish) – population category in genetic studies, AT (allele total) – total number of alleles tested, B – benign, FIN (Finnish) – population category in genetic studies, GERP (genomic evolutionary rate profiling) – a measure of evolutionary conservation of sequences, H – heterogenous, Het – heterozygous, LB – likely benign, LP – likely pathogenic, maxAF (maximum allele frequency) – the highest observed allele frequency across all populations, maxPOP – population in which the maximum allele frequency is observed, MFS – Marfan syndrome, MIMM – moderate impact: missense mutation, N – neoplasm, NFE (non-Finnish European) – population category in genetic studies, P – pathogenic, PhastCons – scores measuring the conservation of sequences across multiple species, SIFT – software tool that predicts whether an amino acid substitution affects protein function, SM – sporadic mutation, VUS – variant of uncertain significance

on routine survivorship follow-up and vigilance for late effects rather than active oncologic intervention.

DISCUSSION

The described case raises two distinct questions – cancer predisposition and treatment-related toxicities. Evidence remains sparse for both, and, critically, there are no comparative data showing that chemotherapy complications are more frequent, more severe, or longer-lasting in patients with MFS than in peers without MFS; we therefore emphasize what is known and where uncertainty persists [7].

Considering cancer risk, current epidemiology does not allow firm conclusions about an increase in malignancies among individuals with Marfan syndrome, and data for childhood leukemias are particularly limited. A nationwide case-control analysis from Taiwan suggested higher overall odds of cancer in Marfan syndrome, whereas subsequent literature consists mainly of case reports and small series that describe unusually early tumor onsets but do not control for surveillance intensity or other confounders. Our case does not establish causality, and we refrain from inferring a syndromic predisposition to pediatric ALL/acute myeloid leukemia (AML); at present, intensified malignancy surveillance is not guideline-supported without further replication [8, 9].

There is no evidence beyond the index patient that MFS modifies the frequency, depth, or duration of chemotherapy-induced neutropenia in pediatric ALL. In general cohorts, grade ≥ 3 neutropenia is expected during intensive blocks with typical neutrophil recovery within weeks; whether Marfan-related alterations in extracellular matrix and transforming growth factor β (TGF-β) signaling influence marrow-niche dynamics remains unknown. Absent comparative data, supportive care and dose-modification practices should follow standard pediatric ALL protocols [7].

The published evidence linking Marfan to sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is limited to an isolated ALL case with unusually early, severe VOD during induction. Outside transplant conditioning and historical drug-related contexts, chemotherapy-associated SOS/VOD in contemporary ALL regimens is uncommon. The modern European Society for Blood and Marrow Transplantation criteria in adults and children frame SOS/VOD as an endothelial-injury disorder and guide risk-adapted management, with defibrotide as the established endothelium-protective therapy. Given *FBN1*'s role in vascular microfibrils and the centrality of endothelial stress in SOS/VOD, a biological intersection is plausible yet remains unproven; current data do not justify regimen changes solely on the basis of MFS [9, 10].

Current evidence does not support enhanced, disease-specific cancer screening for individuals with Marfan syndrome. One population-based study suggested increased malignancy risk, but its findings are not verified and limited; recent reviews emphasize insufficient and heterogeneous data. Professional guidance for MFS focuses on cardiovascular surveillance and does not recommend additional oncologic screening beyond age- and sex-appropriate population protocols. Acute myeloid leukemia/ALL lack validated population screening; intensified hematological surveillance applies only to defined germline predisposition syndromes (e.g., *RUNX1*/*CEBPA*/*GATA2*), not *FBN1*-associated MFS [8, 11, 12].

A rare but repeatedly reported co-occurrence of MFS and malignancies – including leukemia and diffuse large B-cell lymphoma – has been described in case reports and small series; however, a causal association has not been established.

There are few reports in the available literature on the coexistence of MFS and hematological conditions. All identified reports are summarized in a Supplementary Table. Presented reports span a wide age range, from infancy [13] to elderly patients [14]. The table documents a variety of hematological malignancies associated with MFS, including subtypes of acute myeloid leukemia, T-cell prolymphocytic leukemia, diffuse large B-cell lymphoma, Hodgkin lymphoma, and ALL. This diversity suggests no specific predisposition to a single type of malignancy.

In our summary of published cases (Supplementary Table), most reported patients are adults, whereas pediatric observations are scarce. Consequently, the current evidence base is insufficient to draw conclusions about cancer incidence or age at onset in children with MFS.

The treatment of hematological malignancies in MFS patients often leads to severe complications, including pancytopenia, febrile neutropenia, VOD, and can cause fatal outcomes [10, 13, 15]. These findings underscore the importance of vigilant cardiovascular monitoring in MFS patient population, particularly during and after cancer treatment, including stem cell transplantation. They also highlight the need for tailored and careful monitoring of therapeutic protocols to manage the increased risk of adverse effects [10, 16].

One report presented a 51-year-old woman with a pre-existing diagnosis of MFS who developed VOD prior to bone marrow transplantation for T-cell acute-lymphoblastic leukemia (T-ALL) [17]. This was not an isolated finding. Kraemer *et al.* [10] reported a similar case of a 21-year-old male with MFS, T-ALL, and VOD diagnosed post-stem cell transplantation [16, 18, 19]. These observations warrant further investigation into a possible link between MFS and VOD. Marfan syndrome, a connective tissue disorder, can affect blood vessel function throughout the body. We hypothesize that MFS-related vascular abnormalities could predispose individuals to VOD, potentially by impacting liver sinusoidal structure and blood flow, leading to impaired perfusion. This hypothesis, if proven, has significant clinical implications. Chemotherapy, a mainstay of ALL treatment, is primarily

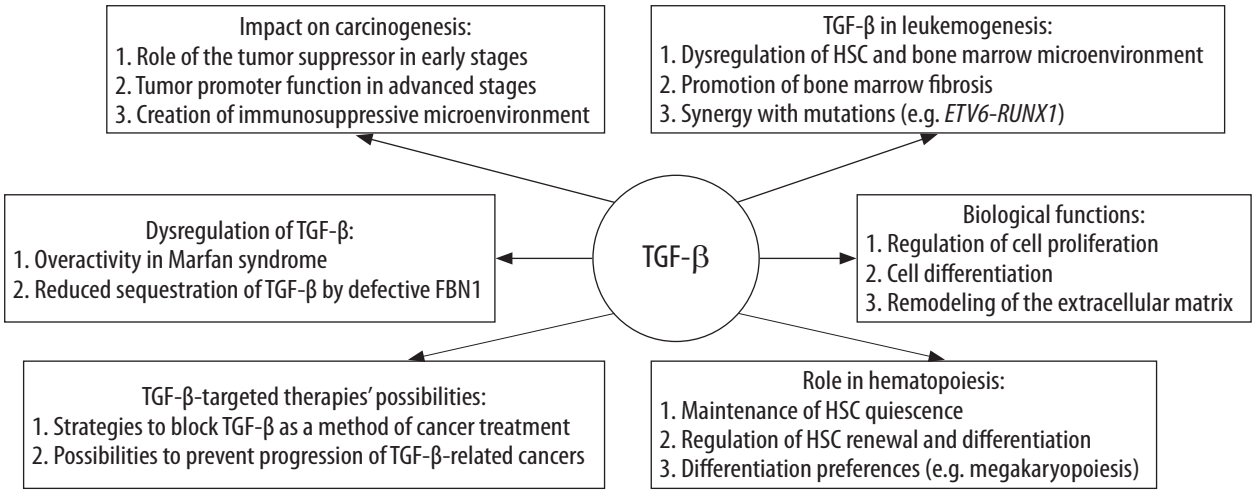

FIGURE 2. Key role of transforming growth factor β

FBN1 – fibrillin-1, HSC – hematopoietic stem cell, TGF-β – transforming growth factor β

metabolized by the liver. Compromised liver function due to underlying VOD could alter drug metabolism, potentially leading to unexpected pharmacokinetics and efficacy/toxicity profiles. This underscores the need for individualized treatment approaches for patients with MFS suffering from hematological and oncological diseases, potentially including pre-emptive measures to mitigate VOD risk and closer monitoring of drug response.

It is also important to consider that the correlation between MFS and leukemia may not be due to a direct genetic link – the occurrence of one genetic disorder can imply the presence of mutations in other genes. Significant insights were gained from the WES study of our patient, which revealed numerous genetic abnormalities potentially associated with both the patient's malignancy and the various complications experienced during treatment. Table 2 presents potentially significant genetic variants that could predispose the patient to therapy complications, a spectrum of complications, the malignancy itself, and the identified gene variants suggest a potential link between clinical symptoms and genetic alterations that are not associated with MFS by itself.

The genetic landscape of ALL, a hematological malignancy characterized by the overproduction of immature WBC, involves a variety of chromosomal rearrangements and gene mutations, some of which could hypothetically interact with MFS-related pathways. The spectrum of cancer predisposing genes was revealed in the WES report (Table 2). For *CHEK2*, there are currently no convincing data supporting an increased risk of pediatric ALL; any link in our case should be seen as a possible, hypothesis-generating association observed by the authors, not as an established effect. *CHEK2*'s role in DNA repair and apoptosis intersects with cellular mechanisms often disrupted in leukemia. This gene's variant, c.573+1G>A, results in a splicing mutation that could significantly impact gene function (ExAC = 0.00016; Het. C/T; rs121908698) [22, 23] and may serve as a criterion for cancer predisposing syndrome (Li-Fraumeni-like syndrome) [20, 21].

Furthermore, variations in *MYH7*, associated with myopathies and cardiomyopathies, might not be directly linked to ALL, but could influence the patient's overall health status and response to ALL treatment due to its role in muscle function and structure (Het. C/G; rs397516171). Similarly, genes such as *AP4B1* (spastic paraplegia 47, Het. CTG/C; rs587779388) and *ACO2* (optic atrophy 9, Het. C/G; rs141772938) are noted for their probable pathogenic status, indicating a potential multifaceted impact on the patient's phenotype [22]. This could be associated with presented side effects of treatment that strongly impact the whole functioning of the patient [23, 24].

In addition to the previously mentioned variants, the WES report identifies many other genetic variants that may explain cancer predisposition, post-treatment complications, and nonspecific dysfunctions. However, this hypothesis requires further comprehensive studies examining the entire exome in the context of cancer treatment complications. It is important to emphasize that excessive reliance on WES results may bring a risk of overinterpretation [18, 22].

We investigated the direct effects of the MFS phenotype and *FBN1* gene-related complications on immune cells. However, *FBN1* expression in both leukemic and non-pathological immune cells was found to be negligible. As illustrated in Figure 2, *FBN1* gene expression in immune cells is minimal and remains at a median level compared to selected tissues with high *FBN1* expression, which are frequently affected by MFS-related pathology. If any impact on immune cells exists, it likely occurs through indirect pathways, such as the previously mentioned TGF-β signaling. One potential explanation for the increased malignancy risk in individuals with MFS, compared to the general population, is their significantly greater exposure to X-ray radiation from diagnostic procedures, such as those assessing aortic health [19].

Although, the last description of two MFS patients with neuroblastoma mentioned no evident higher risk of malignancy in this genetic condition [25]. Another factor could be the immunosuppressive effects of TGF-β, which may reduce the immune system's ability to recognize and eliminate malignant cells, thus promoting tumor growth [26]. These mechanisms remain hypothetical in MFS and have not been demonstrated to shift cancer risk or timing of onset; thus, they should be regarded as avenues for future study rather than established drivers.

The association between MFS and malignancies, although not fully understood, may be related to the significant role of TGF-β, which, when dysregulated, can promote cancer progression [27]. Marfan syndrome is a genetic connective tissue disorder caused by mutations in the *FBN1* gene, leading to defective microfibril formation and dysregulation of TGF-β signaling [28, 29]. Fibrillin-1 is essential for binding latent TGF-β binding proteins (LTBPs), which sequester TGF-β in the extracellular matrix and regulate its bioavailability [29]. In individuals with Marfan syndrome, defective *FBN1* results in decreased sequestration of TGF-β, leading to increased levels of active TGF-β in various tissues [29]. This elevation in TGF-β activity contributes to many of the clinical manifestations of Marfan syndrome, such as skeletal abnormalities, cardiovascular defects, and ocular lens dislocation, due to TGF-β's profound effects on cell proliferation, differentiation, and extracellular matrix remodeling [29].

While TGF-β pathway inhibition is being explored across oncology, there is no evidence to support its use in MFS-associated ALL. Any discussion of TGF-β-directed therapy in this context should be regarded as hypothesis-generating only, not a clinical recommendation.

In the context of leukemogenesis, TGF-β exhibits a complex role, acting as both a tumor suppressor and a tumor promoter depending on the disease stage and cellular context [28, 30, 31]. During early stages of tumorigenesis, TGF-β can inhibit cell proliferation and induce apoptosis in transformed cells, acting as a tumor suppressor [28, 31]. However, as cancer progresses, cells can develop resistance to TGF-β-mediated growth inhibition, often through mutations or alterations in components of the TGF-β signaling pathway [28, 30]. In such cases, cancer cells may exploit TGF-β signaling to promote their survival, proliferation, and metastasis [28, 31]. For example, in AML, leukemic cells may exhibit insensitivity to the inhibitory effects of TGF-β due to mutations in TGF-β receptors or downstream signaling molecules [30]. This insensitivity allows for uncontrolled proliferation of leukemic cells. Additionally, TGF-β can contribute to the development of an immunosuppressive tumor microenvironment by inhibiting the function of various immune cells, such as T-cells, natural killer cells, and macrophages [32]. This immunosuppression allows leukemic cells to evade immune surveillance and promotes disease progression [32]. Moreover, TGF-β can influence the bone marrow niche by promoting fibrosis and altering cytokine production, which can affect normal hematopoiesis and create a microenvironment that supports leukemic cell growth [30]. Elevated TGF-β levels can stimulate the production of extracellular matrix components, leading to bone marrow fibrosis, which is commonly seen in myeloproliferative neoplasms [30]. In patients with MFS, the heightened TGF-β activity due to defective *FBN1* may contribute to an environment conducive to leukemogenesis. Also, this can alter the hematopoietic microenvironment and disrupt normal hematopoietic stem cell (HSC) regulation, potentially leading to the development of leukemia [29, 30, 33]. The dysregulated TGF-β signaling may push HSCs towards differentiation, depleting the stem cell pool and causing compensatory proliferation, which increases the risk of genetic mutations and malignant transformation [27, 30]. Furthermore, the immunosuppressive effects of elevated TGF-β can impair immune surveillance, allowing pre-leukemic clones to expand unchecked [32]. The combination of altered HSC regulation, bone marrow microenvironment changes, and immune suppression may synergistically contribute to the development and progression of leukemia in individuals with MFS. Additionally, the *ETV6-RUNX1* fusion gene, resulting from the t(12;21)(p13;q22) chromosomal translocation, is one of the most common genetic alterations in pediatric ALL [33] and was presented in our patient. This fusion interferes with normal *RUNX1* function, a critical transcription factor for HSC differentiation, contributing to leukemogenesis [33]. Dysregulated TGF-β signaling in MFS may interact with the *ETV6-RUNX1* fusion to promote the survival and proliferation of pre-leukemic cells [33]. Elevated TGF-β levels could inhibit the proliferation of normal progenitor B-cells while having minimal effects on ETV6-RUNX1-positive cells, thus favoring their competitive expansion. Therefore, the combination of TGF-β dysregulation in MFS and the presence of the *ETV6-RUNX1* fusion may increase the risk of leukemia development, underscoring the need for further research into this interplay.

No additional actionable kinase-activating lesions (e.g., BCR-ABL1 or ABL-class fusions) were identified which would support use of tyrosine-kinase inhibitors; thus, targeted therapy was not indicated for this genomic profile [34, 35].

TARGETED AND IMMUNE THERAPIES IN PEDIATRIC B-ALL: SCOPE, INDICATIONS, AND GAPS RELEVANT TO THE PRESENT CASE

In contemporary pediatric B-ALL, several targeted or immune-based approaches improve outcomes in defined settings:

- tyrosine-kinase inhibitors for BCR-ABL1 – positive disease and for a subset of ABL-class "Ph-like" fusions (e.g., ABL1/2, PDGFRB, CSF1R) integrated with chemotherapy,

- CD19-directed bispecific T-cell engager blinatumomab, which improves event-free/disease-free survival vs. conventional chemotherapy in children with B-ALL in relapse or with measurable residual disease,
- CD22-directed antibody – drug conjugate inotuzumab ozogamicin with meaningful response rates in pediatric relapsed/refractory B-ALL,
- CD19 CAR-T-cells (tisagenlecleucel) inducing high remission rates in relapsed/refractory pediatric and adolescent and young adult B-ALL.

By contrast, there is no approved agent that specifically targets the *ETV6-RUNX1* fusion, and standard risk-adapted chemotherapy remains the backbone for this genomic subtype. Accordingly, in cases like ours (*ETV6-RUNX1*), "targeted therapy" should be regarded as contingent on actionable lesions (e.g., BCR-ABL1 or ABL-class fusions) or disease stage (relapse) rather than as a generalizable recommendation [34–37].

While TGF-β pathway inhibition is being actively explored across oncology and fibrosis, clinical data in pediatric ALL are limited and there are no trials specific to MFS or to *ETV6-RUNX1* B-ALL. Thus, any reference to TGF-β–directed strategies in the present context should be regarded as hypothesis-generating only, not as a treatment recommendation [38, 39].

A key limitation of this study is the absence of parental data; without segregation or de novo assessment, *MYH7* and other prioritized variants remain classified as variant of uncertain significance under American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria. In addition, our literature synthesis relies predominantly on heterogeneous case reports with a clear adult predominance and likely publication bias, which precludes conclusions regarding cancer risk or the timing of onset in Marfan syndrome.

CONCLUSIONS

This case illustrates the complexity of managing pre-B-ALL in a child with MFS, requiring individualized treatment planning and vigilant toxicity surveillance. The report does not establish that MFS predisposes to malignancy or modifies the timing of leukemia onset. Rather, it underscores diagnostic and therapeutic challenges when an inherited connective-tissue disorder co-occurs with hematological cancer, and highlights the need for prospective, genotype-informed studies to clarify any true association and to determine whether MFS influences toxicity profiles or outcomes.

DISCLOSURES

1. Institutional review board statement: The patient was treated according to the International Study for Relapse of Childhood ALL 2010 standard-risk (IntReALL-2010 SR) protocol.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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