# Li Fraumeni syndrome presenting atypically as Immune thrombocytopenia and early aging phenotype-A case report

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## Abstract

**Background:** Germline mutations in the **TP53** gene are primarily associated with Li-Fraumeni syndrome (LFS), a hereditary cancer predisposition disorder. While the predominant manifestations are various malignancies, there is limited information regarding non-malignant clinical features, particularly affecting the skin and musculoskeletal systems, in TP53 mutation carriers. We report a rare case of LFS presenting with immune thrombocytopenia (ITP) and changes of early aging and discuss the possible underlying pathophysiological mechanisms for these.

**Case presentation:** A 16-year-old female presented with complaints of spontaneous ecchymotic patches over both upper limbs, lower limbs, and chest along with menorrhagia. Comprehensive evaluation with bone marrow examination confirmed diagnosis of ITP which was treated with steroids, intravenous immunoglobulin, and thrombopoietin receptor agonists, and the patient responded completely with normalization of platelet count. Given the positive family history of thrombocytopenia in the sister and early malignancy in the maternal family, a whole exome sequencing was done which showed a heterozygous pathogenic variant in the TP53 gene confirming the background of LFS.

**Conclusion:** A case of LFS with a positive family history presenting as primary ITP successfully managed with ITP-like treatment is a rare immunological complication and has not been reported in the literature to date.

**Keywords:** Case report, Li Fraumeni syndrome, TP53 mutation, Immune thrombocytopenia, familial cancer syndrome

**Type of Article:** CASE REPORT **Specialty:** Hematology

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## Background

**TP53** mutations are strongly associated with both hereditary and sporadic cancers. Germline *TP53* mutations cause Li-Fraumeni syndrome **(LFS)**, a cancer predisposition disorder characterized by a high lifetime risk of multiple malignancies, including **breast cancer**, **soft tissue sarcomas**, **osteosarcoma**, **brain tumors** (choroid plexus carcinoma and medulloblastoma), **adrenocortical carcinoma**, **leukemia (acute lymphoblastic leukemia** and **acute myeloid leukemia)**, **lung cancer**, and **gastrointestinal cancers** [1]. The **TP53 gene** encodes the **p53 protein**, a crucial tumor suppressor that regulates cell cycle arrest, apoptosis, and DNA repair in response to cellular stress. Unlike other tumor suppressor genes that have a higher proportion of frameshift and nonsense variants, *TP53* has mainly missense variants located at certain hotspots. Two published algorithms are utilized to identify patients at risk of LFS who would benefit from molecular testing, the classical LFS criteria and the Chompret criteria [2,3]. There are no specific, observable non-cancerous symptoms that have been commonly found associated directly with this syndrome. However, individuals with LFS might exhibit findings like atypical moles or benign skin lesions during routine cancer screenings [4]. Diagnosing non-cancerous presentation of LFS like ITP is crucial for clinicians and hemato-oncologists as these patients can have critical bleeds if not treated appropriately on time. To the best of our knowledge, we report the first case of LFS presenting with primary ITP and changes of early aging and discuss the possible underlying pathophysiological mechanisms for these.

## Timeline

### *Patient information*

A 16-year-old female of Indian Ancestry from Mombasa, Kenya started to notice spontaneous ecchymotic patches over both upper limb, lower limb, and chest along with menorrhagia in April 2024. Further evaluation done in Kenya showed hemoglobin 8 gm%, total leucocyte count

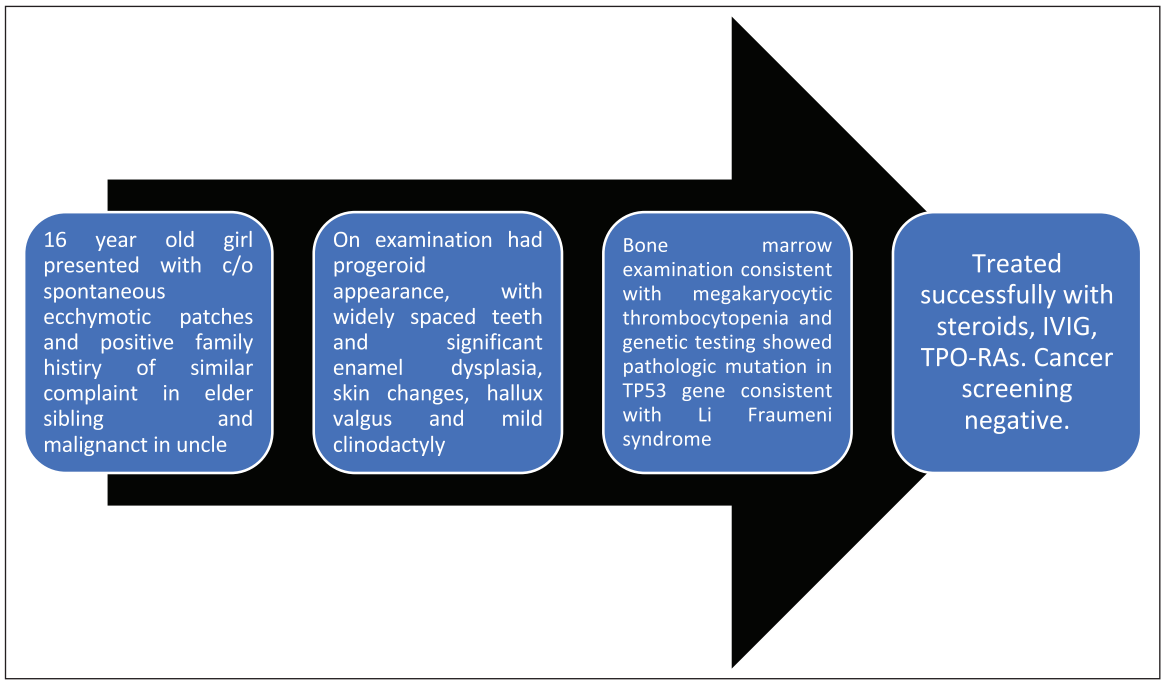


***Figure 1.*** *Timeline of events.*


***Figure 2.*** *a,b. Widely spaced teeth with enamel dysplasia; c,d,e. Hyperkeratotic skin over the dorsum of hands, feet, and knee joint; f. Ulnar deviation of the wrist.*

5,900/mm$^3$ with a normal differential, and platelet count 4 x10$^9$/L. She was transfused two single donor platelets and two red cell concentrates. Platelet counts increased to 56 x 10$^9$/L post transfusion and she was referred to Nairobi for consultation with hemato-oncologist.

In Nairobi, she was suspected to have ITP and was initially treated with pulse dexamethasone 20 mg daily for 4 days but there was no significant response. After that, she received an intravenous immunoglobulin (IVIG) infusion at a dose of 2gm/kg divided over 4 days, to which she had a modest response, with platelet count steadily rising from 6x10$^9$/L to 36 x10$^9$/L over 4 days. She was then referred to India for further treatment.

On arrival to India, detailed history-taking revealed that she was born to fourth-degree consanguineous parents. Her younger sister died at the age of 15 months while undergoing investigation for thrombocytopenia. There is a family history of acute lymphoblastic leukemia in a maternal uncle at the age of 13 years. Her maternal aunt passed away due to an underlying congenital heart disease.

## *Physical examination*

On examination, she had a bulbous nasal tip with an overhanging columella a progeroid appearance, widely spaced teeth, and significant enamel dysplasia (Figure 2a, b). The skin was hyperkeratotic with punctate depigmentation (Figure 2c–e). Hyperlaxity of interphalangeal and

metacarpophalangeal joints along with mild ulnar deviation of both wrists (Figure 2f) was present on musculoskeletal examination. There was bilateral hallux valgus and mild clinodactyly. Anthropometric parameters and pubertal development were appropriate. Systemic examination was unremarkable.

## Diagnosis

Her bone marrow aspirate and trephine biopsy showed normocellular marrow with adequate megakaryocytes consistent with megakaryocytic thrombocytopenia. Erythrocyte sedimentation rate and ferritin were high while lipid profile and echocardiography were normal. Anti-neutrophilic antibody (ANA) was negative and the ultrasound abdomen was normal. Chromosomal analysis showed a normal female karyotype and stress cytogenetics was negative for increased chromosomal breakage.

### *Assessment*

A whole exome sequencing done to rule out an underlying syndromic disorder because of a positive family history revealed a heterozygous pathogenic variant- TP53:c.524G>A;p.(Arg175His) implicated in the causation of the LFS (OMIM:#151623). Two additional variants unrelated to the patient's phenotype were detected. The details of the different variants identified and parental variant segregation have been summarized in Table 1.

### *Intervention*

Based on a comprehensive evaluation she was confirmed to have ITP. As the platelet counts were critically low and there was a suboptimal response to steroids in Kenya, she was treated with a combination of IVIG (400 mg/kg/day given for 5 days) along with Eltrombopag 50 mg once a day. Initially, the platelet count increased to 51x10$^9$/L but again dropped critically to 9 x10$^9$/L. Therefore, she was given 2$^{nd}$ course of IVIG (500 mg/kg/day for 4 days) and was started on oral methylprednisolone (1mg/kg/day) and Inj. Romiplostim (5 microgram/kg subcutaneously once a week) as her ITP was refractory. Her platelets showed an increasing trend (max platelet count 221x10$^9$) with the above treatment. Romiplostim was stopped after 9 doses and Eltrombopag was continued along with a tapering dose of steroid.

### *Follow-up and outcomes*

MRI done for cancer screening showed no evidence of overt malignancies.

Genetic counseling was offered and a surveillance plan for cancer screening and risk reduction was explained.

On parental testing, both parents were heterozygous for the *CFH* variant, the mother was heterozygous for the *APOB* variant and the *TP53* variant was de novo in the index patient.

**Table 1.** Description of variants identified in whole exome sequencing of the patient

| GENE/ TRANSCRIPT | VARIANT | PROTEIN CHANGE | VARIANT CLASSIFICATION | ZYGOSITY | DISORDER (OMIM NUMBER) | MODE OF INHERITANCE | MAIN PHENOTYPE OF DISEASE | PARENTAL SEGREGATION |
|---|---|---|---|---|---|---|---|---|
| *TP53* (NM_000546) | c.524G>A | p.(Arg175His) | Pathogenic | Heterozygous | Li-Fraumeni syndrome (OMIM:#151623). | AD | Cancer predisposition | Absent in both parents |
| *APOB* (NM_000384) | c.8538dup | p.(Gly2847Trpfs*5) | Likely Pathogenic | Heterozygous | Hypobetalipoproteinemia, familial, 1 (OMIM:#615558) | AR | Retinal degeneration, ataxia, abetalipoproteinemia | Present in mother |
| *CFH* (NM_000186) | c.3226C>G | p.(Gln1076Glu) | Uncertain significance | Homozygous | Hemolytic Uremic Syndrome, atypical susceptibility to 1 (OMIM: #235400) | AR | Hypertension, renal failure, seizures, hemiparesis | Present in both parents |

AD- Autosomal dominant, AR- Autosomal recessive, c-complementary DNA sequence, p- protein sequence, OMIM- Online Mendelian Inheritance in Man

The patient was sent back to Kenya on Methylprednisolone 12 mg/day and Eltrombopag 100 mg/day. (Figure 1)

## Discussion

TP53 mutations cause LFS that exhibit high penetrance, with lifetime cancer risk estimates reaching approximately **90% in women** and **73% in men by age 60 years** [5]. Noncancerous presentation in such patients remains poorly reported and understood. Our case highlights the benign presentation of LFS where the patient presented as a classic case of megakaryocytic thrombocytopenia and responded to the treatment.

The p53 protein consists of key domains: a **transactivation domain** (regulates gene expression), a **DNA-binding domain** (DBD), and an **oligomerization domain** (essential for tetramer formation and function) [6]. The **mutation identified in our patient** lies in the **DBD** (residues 102-292), which is the most important domain. This mutation disrupts p53's ability to bind DNA and regulate target genes, leading to the loss of its natural tumor suppressor function and causing a novel gain of function instead [7]. This gain of function mutation induces genetic instability by impairing the DNA repair by hindering the recruitment of other double-strand break repair proteins like MRN/ATM (Mre11-Rad50-Nbs1 complex/Ataxia-telangiectasia) [8]. The mutant p53-Arg175His activates many genes like a guanine exchange factor-H1 for RhoA (*GEF-H1*), and growth-regulated oncogene 1 (*GRO-1*) thereby promoting tumor growth and proliferation [9,10]. The p53-Arg175His also increases tumor migration, and metastasis and promotes resistance to many chemotherapeutic agents and angiogenesis [11,12].

While the role of p53 in tumor suppression by inducing cell cycle arrest, senescence, apoptosis, and DNA repair is well established, there is emerging evidence of its role in autoimmunity. p53 plays a protective role against various systemic autoimmune diseases by suppressing cytokine production and reducing the number of pathogenic cells. It helps strike a balance between Th17 cells and Tregs, crucial to preventing the development of autoimmune diseases [13].

Autoimmune thrombocytopenia in LFS has not been reported previously. Consequently, the underlying mechanisms need to be understood. In one study, exploring the role of microRNAs (miRNA) in autoimmune thrombocytopenia and megakaryopoiesis, one specific miRNA (miR-98-5p), has been found to upregulate p53 expression by inhibiting the p53 ubiquitination. Studies have also reported that miR-98-5p expression also leads to increased apoptosis of mesenchymal stem cells in ITP patients [14]. However, whether *TP53* mutations are associated with the upregulation of miR-98-5p or not is an area of research. These findings may provide us with a link between p53 mutations and ITP.

In a recent study on autoimmune disorders prevalence in LFS patients, none of the 11 (out of 115) LFS patients with autoimmune manifestations, reported thrombocytopenia [15].

The pro-senescent and pro-apoptotic effects of p-53 have been elucidated previously [16]. This may be responsible for the early aging phenotype seen in our patient. An active p53 induces the expression of pro-senescence targets like p21, which facilitates G1 cell cycle arrest, and E2F7, which represses mitotic genes. Additionally, p53 influences other aging-related pathways, including reactive oxygen species (ROS) production and mTOR signaling. While baseline p53 levels help mitigate oxidative damage by reducing ROS, an overactivated p53 increases intracellular ROS, contributing to its pro-apoptotic and pro-senescent effects [16]. However, the precise mechanism of p53-mediated early aging and senescence remains incompletely understood.

This being a case report the generalizability is limited more so because this case is the first of its kind. However, it emphasizes the need for scrutiny of such manifestations as ITP. Acute thrombocytopenia and intracranial hemorrhage (ICH) can often be fatal in such cases. Also, menorrhagia in girls can be alarming and challenging to treat.

## Conclusion

We report a rare case of LFS diagnosed after the primary presentation as ITP without any underlying malignancy, successfully treated with steroids, intravenous immunoglobulin, and thrombopoietin receptor agonists. The possibility of ITP in LFS and its potential deleterious consequences such as ICH and bleeding manifestation elsewhere needs to be highlighted for early intervention and management. Literature on non-neoplastic manifestations of *TP53* mutations is sparse and our report highlights one of them. These patients need regular surveillance for the occurrence of various malignancies due to reduced p53 activity.

### What is new

The authors report a case of Li Fraumeni syndrome diagnosed in a case of primary immune thrombocytopenia and changes of early aging on examination. They also discuss the possible underlying pathophysiological mechanisms for these which are rarely reported in the literature.

## List of abbreviations

| | |
|---|---|
| ANA | Anti-neutrophilic antibody |
| ATM | Ataxia-telangiectasia |
| DBD | DNA-binding domain |
| GEF-H1 | Guanine exchange factor-H1 for RhoA |
| GRO-1 | Growth-regulated oncogene 1 |
| ICH | Intracranial hemorrhage |
| ITP | Immune thrombocytopenia |
| IVIG | Intravenous immunoglobulin |
| LFS | Li-Fraumeni syndrome |

| | |
|---|---|
| miRNA | micro RNA |
| MRN | Mre11-Rad50-Nbs1 complex |
| ROS | Reactive oxygen species |
| TPO-RAs | Thrombopoietin receptor agonists |

## Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

## Consent for publication
Written informed consent was obtained from the parents.

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## Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

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## Summary of case

| | | |
|---|---|---|
| 1 | Patient (gender, age) | 16 years, female |
| 2 | Final diagnosis | Li Fraumeni syndrome with immune thrombocytopenia |
| 3 | Symptoms | Low platelets with mucosal bleeds and ecchymosis |
| 4 | Medications | Steroids, Thrombopoietin receptor agonists |
| 5 | Clinical procedure | None |
| 6 | Specialty | Haemato-Oncology |