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CASE REPORT

From severe aplastic anemia with TERT variant to Wilson disease - associations or not

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Abstract
Severe aplastic anemia is a life-threatening ineffective hematopoiesis, arising from inherited or acquired traits. Wilson disease is a rare congenital metabolic disorder with copper accumulation. Here we report a rare case of a 15-year-old boy, who presented with bone marrow failure. Whole exome sequencing revealed several gene mutations in ATP7B and TERT. Based on the phenotypes, telomere lengths and pedigree of his family, the patient was diagnosed with severe aplastic anemia accompanied by Wilson disease. Allogeneic hematopoietic stem cell transplantation and anti-copper therapy helped him achieve transfusion independence and restore relatively normal copper metabolism. We discussed the possible associations between the two rare conditions and optimal management in this situation.

Keywords Aplastic anemia · Wilson disease · Telomere length · Short telomere syndrome · Hematopoietic stem cell transplantation

Introduction

Aplastic anemia(AA), characterized by pancytopenia resulting from bone marrow failure (BMF) [1], is categorized into congenital and acquired AA. Yet differentiation between the two categories remains a bit difficult for young patients as both may present short telomere length (TL) and gene mutations. Replacement of a failed bone marrow is curative of the underlying disease, while immunosuppression and stem cell stimulation may work on acquired AA because of the immune-mediated mechanism.

Hepatolenticular degeneration, known as Wilson Disease (WD), is an inherited disorder characterized by the pathological accumulation of copper in the liver, brain and other organs. It is caused by mutations in ATP7B, and the clinical course varies in the type and severity of symptoms [2]. The management strategies include copper chelators, liver transplantation and symptomatic treatment when symptoms of deteriorating neurological systems and other organs are present.

AA and WD are both rare conditions, so far, there was no case reported on one individual and the association remained a mist. Here we report a patient with transfusion-dependent AA accompanied with WD. He later achieved transfusion independence and restoration of normal copper metabolism after allogeneic hematopoietic stem cell transplantation (Allo-HSCT) combined with copper chelation therapy.

Materials and methods

Clinical and biochemical data collection

Clinical data was collected through a medical record from the Department of Hematology, Tianjin Medical University General Hospital, China. The study was conducted in

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accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Tianjin Medical University General Hospital. Informed consent was obtained from the subject involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Biochemical testing

Measurements of plasma liver enzymes, coagulation time, bacteriology and virology tests and Complete Blood Count were conducted in comprehensive laboratories in Tianjin Medical University General Hospital according to standard procedures.

Hematopoietic stem cell transplantation

Patient was conditioned with a BFAC regimen before receiving haploidentical donor HSCT (HID-HSCT) [3]. The donor was the patient's father, aged 37, HLA-matched (7/10), negative donor-specific anti-HLA antibody (DSA). The autonomous consent free from coercion was obtained from the donor. The BFAC conditioning regimen was composed of busulfan (BU 6.4 mg/kg) i.v. in divided doses on days −8 to -7, fludarabine (FLU 150 mg/m2) i.v. in divided doses on days −6 to -2, cyclophosphamide (CY 150 mg/kg) i.v. in divided doses on days −5 to -2, and rabbit Antithymocyte Globulin (r-ATG) (Genzyme, Cambridge, MA, USA, 12.5 mg/kg) in divided doses on days −6 to -2. Peripheral blood stem cells ($CD34^+$ 3.5×10^6/kg) were infused on day 0. For graft versus host disease (GVHD) prophylaxis, CsA (approximately 2 mg/kg/d i.v.) with the goal serum level of 200 to 300 ng/ml was started on day −8, Methotrexate (MTX, 15 mg/m2/d on day+1, 10 mg/m2/d on days+3, +6, +11) and Mycophenolate (MMF, 1 g/d on days −8 to +30) were administrated. Neutrophil engraftment occurred on day+20, platelet engraftment occurred on day+29.

Whole exome sequencing (WES)

DNA was extracted from the blood samples of the patient, his parents and sister from the using the QIAGEN Blood Mini Kit. Genomic DNA was subjected to WES using a commercial service provided by Guangzhou Kingmed Diagnostics Group Co., Ltd, China. Exonic DNA libraries were enriched using the Illumina TruSeq Exome Library Prep Kit, and sequenced on an Illumina NovaSeq platform. Sequence reads were aligned to the human genome using the SOAP Aligner (v2.21) software, generating genotypes for each position in the target region. All pathogenic and likely pathogenic variants detected by WES were confirmed by Sanger sequencing. Variant classification was performed according to the ACMG guidelines [4].

Results

Case report

A 15-year-old male teenager was admitted into our center presenting with "petechiae over his entire body for 1 week". Physical examination revealed scattered, pinhead-sized petechiae on the surfaces of his limbs and shoulder-neck and abdomen region, visible pigmentation on the chest and abdomen. No enlargement of superficial lymph nodes or hepatosplenomegaly was palpable. The patient reported no serious past medical history. He had not been exposed to any specific medications or radiations since birth. His family members, including his parents and younger sister, were also in good health. Upon admission, blood routine tests indicated anemia and severe thrombocytopenia (Hb 84 g/L, RBC 3.42×10^{12}/L, Ret 1%, MCV 86 fl., PLT 9×10^9/L, WBC 9.95×10^9/L, Neutrophil 10%, Lymphocyte 88%, Monocyte 2%).

Further examination revealed no abnormalities in the coagulation system, liver and kidney function, thyroid function, bacteriology and virology tests (hepatitis viruses, Epstein-Barr virus, cytomegalovirus, and parvovirus B19) and rheumatological spectrum antibodies. The patient's liver enzymes including alanine transaminase (ALT, 36U/L), aspartate aminotransferase (AST, 19U/L), gamma-glutamyl transferase (GGT, 38U/L) were normalized. Other laboratory tests revealed no obvious liver dysfunction with normal albumin (43 g/L), serum total bilirubin (TBil, 11.2 µmol/L), prothrombin time (PT, 10.4s) and thrombin time(TT, 20.5s). The materials for hematopoiesis including iron, folate, vitamin B12 and erythropoietin were within normal ranges. Platelet glycoprotein-specific autoantibodies were negative. Thrombopoietin (TPO) level was 1605.12 pg/mL (↑) (ref:7–99 pg/mL).

Bone marrow biopsy from ilium showed hypoplasia (Fig. 1A-B). Megakaryocytes were occasionally observed (only 11 megakaryocytes on the entire smear, including 7 primitive ones and 4 non-platelet-producing ones), and no abnormal cells were found on the bone marrow smear (Fig. 1C-D). The Fluorescence In Situ Hybridization (FISH) analysis of the bone marrow for the following abnormalities: [del(5q), del(5), del(7), del(7q), del(20q), +8, -Y, P53], yielded negative results. Immunoglobulin gene rearrangement was negative. Flow cytometry analysis revealed no immature cell populations, no paroxysmal nocturnal hemoglobinuria (PNH) clones or any suspicious markers related to large granular lymphocyte leukemia. Based on the aforementioned examinations, the patient was primarily diagnosed with severe aplastic anemia (SAA).

Tests for Fanconi anemia(FA) [5] including Comet (comet cell rate: 15%, tail moment: 2.09, Olive tail moment:

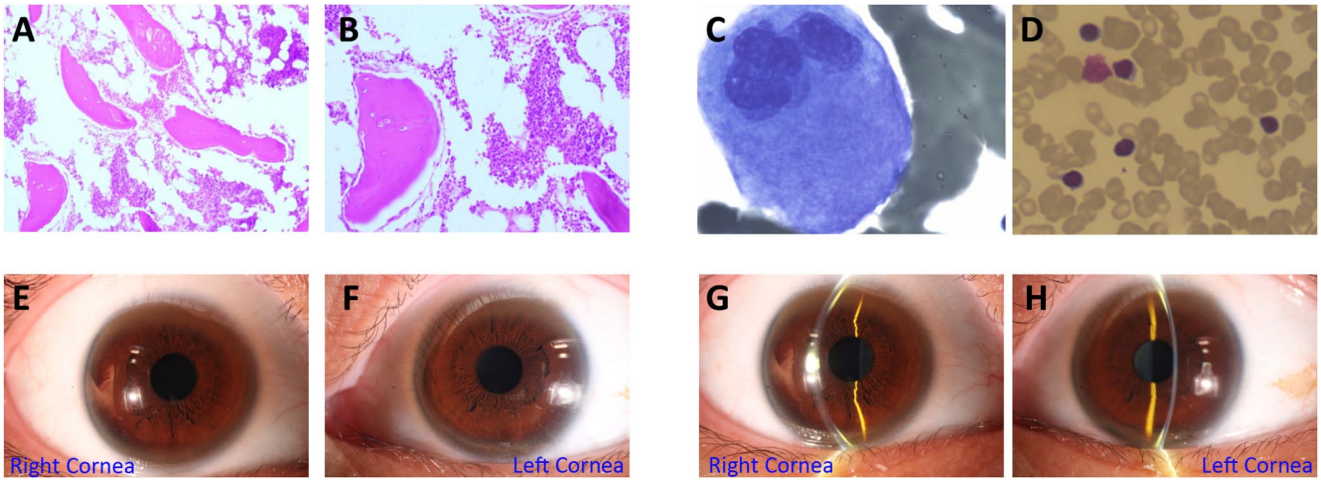

Fig. 1 Bone marrow presentation(**A-D**) and K-F rings(**E-H**). (**A**) Histopathology (HE staining, 4×) (**B**)Histopathology (10×) (**C-D**) Smear (Wright-Giemsa staining, 100×) (**C**)showed A non-platelet-producing megakaryocyte (D) showed relatively high percentage of lymphocytes. (**E-F**)Clinical photograph of the patient's corneas. (**G-H**)Slit lamp images of K-F rings

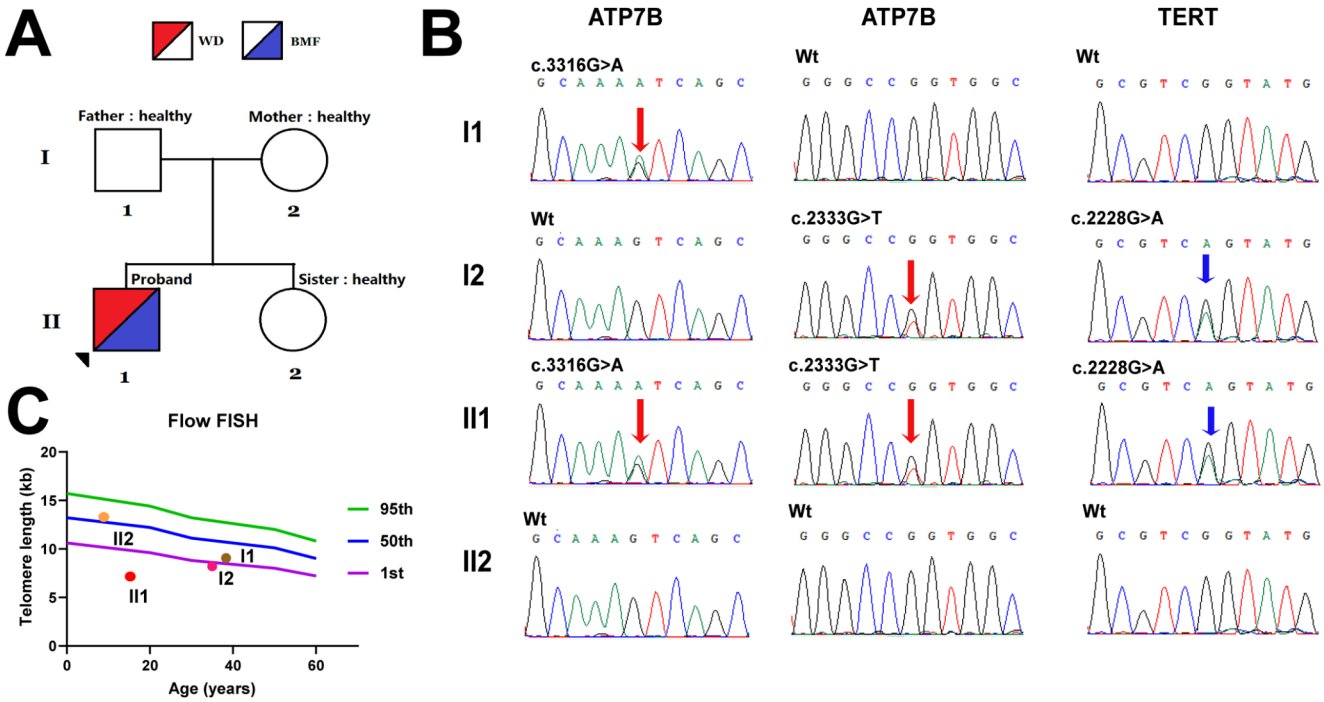

Fig. 2 Pedigree and genomic mutations of the family of the patient with both WD and BMF. (**A**) Pedigree. Arrow indicated the proband (II1) who was the patient. (**B**) Sanger sequencing. The red arrow indicated the heterozygous mutations of ATP7B, the blue arrow indicated the heterozygous mutation of TERT. (**C**) Telomere lenths of the family by Flow FISH. WD: Wilson Disease, BMF: Bone Marrow Failure. Wt: Wildtype

1.65; no apoptotic cells observed.) and MMC chromosomal aberration yielded normal results. Whole-exome sequencing (WES) revealed (Fig. 2B): ① Two pathogenic variants in the ATP7B gene on chromosome 13, including a c.3316G>A variant (p.Val1106Ile) in exon 15 and a c.2333G>T variant (p.Arg778Leu) in exon 8 of the homologous chromosome. The former variant was inherited from the father, and the latter from the mother. ② A variant of unknown clinical significance in the TERT gene on chromosome 5, specifically a c.2228G>A variant (p.Arg743Gln) in exon 6. This site harbored a heterozygous variant inherited from the mother.

Mutations in the copper-transporting ATPase β (ATP7B) gene can lead to impaired bile excretion and subsequent copper metabolism disorders, triggering WD. Additional laboratory tests regarding WD were positive (Table 1).

Table 1 Laboratory tests before and after copper chelation

Tests	admission	6 m since copper chelation	1y since copper chelation	ref
Ceruloplasmin	6.73 ↓	7.14 ↓	16.53 ↓	22 ~ 58 mg/dl
24-hour urine copper	169.5↑	144.7↑	72.6↑	15–60 μg/24 h
Liver stiffness (Fibro touch)	8.5↑	7.5 ↑	7.2	0 ~ 7.3 kPa
Telomere Length	7.5 ↓	7.4 ↓	7.7 ↓	9.6 ~ 14.4 kb

Ophthalmology evaluation found Kayser-Fleischer (K-F) rings bilaterally (Fig. 1E-H). Liver ultrasound showed hepatomegaly with enhanced echogenicity of the liver parenchyma and no clear delineation of intrahepatic ductal structures. Prompted by mutations of ATP7B, early diagnosis of WD [6] initiated the copper chelation therapy. Given the risk of bone marrow suppression associated with D-penicillamine (DPA), the patient was treated with dimercaptosuccinic acid (orally) and sodium dimercaptopropanesulfonate (intravenously) [7] along with copper-limited diet and zinc intake. After 6 months of anti-copper therapy, the patient's laboratory tests had been improved (Table 1).

In addition to WD, the patient was suspected to be with Short Telomere Syndrome (STS), as mutation of telomerase reverse transcriptase (TERT) can trigger a series of STSs, often dyskeratosis congenita(DC), manifested as BMF, dyskeratosis, and tissue fibrosis, with severity varying greatly among individuals [8]. Further detection of TL in peripheral blood nucleated cells using Flow-FISH revealed the TL of the patient was shortened (Fig. 2C). One thing to mention, TL didn't recover after anti-copper therapy (Table 1), which is worth contemplating in the Discussion section.

Clinical course and treatment

Upon admission, the patient was treated with high-dose glucocorticoids and intravenous immunoglobulin (IvIg), followed by an increasing dose of eltrombopag up to 150 mg/day. Failing to respond to previous treatment for 8 weeks, the patient underwent a bone marrow aspiration from sternum, which showed similar results to the one from ilium 2 months ago: hypoplasia with only 3 megakaryocytes observed on the entire smear. Two months after admission, Immunosuppressive therapy (IST) was given. For the 5 months upon admission, the patient was dependent on blood transfusion, as the platelet count fluctuated between (2–40) × 10^9/L, hemoglobin between (36–81) g/L, until he received Allo-HSCT (Fig. 3), as described in "Materials and methods" section. During the 7-month follow-up after Allo-HSCT, the patient has maintained normal copper metabolism and achieved independence from blood transfusions. Post-transplant bone marrow evaluation demonstrated complete hematopoietic reconstitution with hypercellular marrow.

Discussion

WES revealed that the patient harbored mutations in two rare genetic diseases: WD caused by ATP7B mutations and STS by TERT mutations. Both disorders presenting with multiple manifestations made diagnoses challenging, highlighting the importance of genetic disease screening in such young patients.

AA

TERT is involved in the regulation of TL and has significant associations with biological lifespan, tumorigenesis, and immunity [9]. Previous literature revealed a very short TL is defined as < 1st percentile in two or more subsets of lymphocytes as detected by Flow-FISH - the gold standard technique [10]. Although TL can be affected by multiple causes such as genetic background, sex and even ethnicity [11], it is particularly evident in the disease of DC [12]. In DC, there are two life threatening disease manifestations: BMF [13] and cancers. While few literatures reported the short TL and TERT mutations were described in acquired AA [14], the definitive association is still needed to be revealed in large cohorts. In this case, the patient presented with BMF and pigmentation on the skin but did not exhibit the complete DC triad, which contains nail dystrophy and mucous membrane leukoplakia. Unlike the majority of AA patients, who have at least partially response to IST [1], our patient failed but recovered fully from Allo-HSCT. Therefore, two possible explanations might be elicited: One, the patient was with congenital STS such as DC; Two, the patient was with acquired AA. Both diagnoses can easily masquerade as one another, since BMF due to DC, historically characterized by associated physical anomalies, might be present in otherwise phenotypically normal adults [15].

In this case, TERT: c.2228G > A(p.Arg743Gln) is assessed as a variant of uncertain significance (PP3 + PM2_Supporting + PP4) according to the ACMG guidelines [4]. As of April 2025, the frequency of this variant in the gnomAD database is 0.00003, and it is not yet listed in the HGMD database. The variant has been included in the ClinVar database with an overall classification of "conflicting interpretations of clinical significance" (three different laboratories have classified the variant as "uncertain significance," "uncertain significance," and "likely benign," respectively).

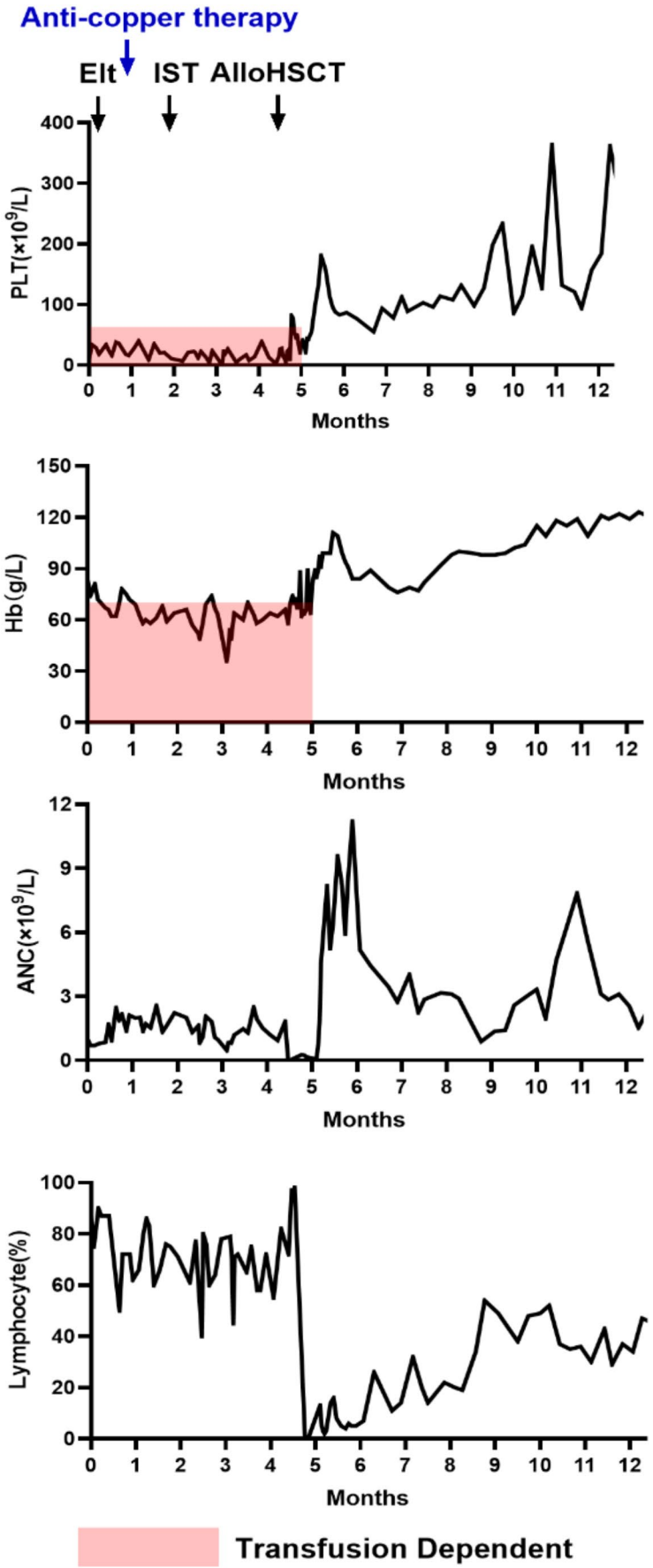

Fig. 3 Platelet (PLT), Hemoglobin (Hb), Absolute Neutrophil Count (ANC) and Lymphocyte(%) change with therapies. Elt: Eltrobapag, IST: Immunosuppressive Therapy, AlloHSCT: Allogeneic Hematopoietic Stem Cell Transplantation

Therefore, the patient was diagnosed with acquired AA for now. This phenomenon was also reported previously, when shorter TL due to the presence of hypomorphic alleles of telomere biology genes influenced the response to IST and eventually led to clonal evolutions [16] like myelodysplastic syndrome or acute myeloid leukemia. Thus in this case, allo-HSCT [17]was a more suitable treatment compared to IST.

WD

Wilson's disease is an autosomal-recessive disorder of copper metabolism caused by mutations in ATP7B [18], afflicting approximately 1 in 40,000 people, with approximately 1 carrier for every 100 people [19]. Its clinical manifestations are complex and diverse, primarily affecting the liver and nervous system, with other symptoms such as ocular abnormalities, hemolysis, renal impairment and bone abnormalities. In this case, the teenager presented with low ceruloplasmin (CP) level, high urinary copper excretion, increased liver stiffness by Fibro-touch and two heterozygous mutations of ATP7B genes located on chromosome 13. Applying the Leipzig scoring system of 2001 [2, 20], WD was diagnosed. This asymptomatic patient, only manifested hepatomegaly and liver steatosis, if undiscovered, might soon develop symptomatic WD [19]. Previous studies have suggested that children with early diagnosis of WD were mostly asymptomatic, especially in China [21]. These patientsmainly have neurological manifestations, which are often seen in late progression [22].

From AA to WD

To our knowledge, this is the first time to report a patient with AA accompanied with WD, two rare conditions in one individual. Very few cases of WD patients with pancytopenia were reported, yet the main cause was copper metabolism disorder [23], and somehow pancytopenia could be reversable [24]. However, whether there is an inner relationship between BMF and WD aroused our interest. In other words, a question was raised: whether the patient with WD was prone to AA or there was no relations between WD and AA whatsoever?

Copper poisoning mimicked by WD may damage erythrocytes and manifest as Coombs-negative hemolytic anemia [2], because copper inhibits sulfhydryl groups of glucose-6-phosphate dehydrogenase and glutathione reductase. Therefore, erythrocytes' cellular antioxidant capacity was reduced, leading to copper-induced hemolysis [25].

Although hemolysis may be seen in WD, anothermechanism of anemia was explained by iron deficiency. The copper-dependent ferroxidase CP, which mobilizes iron through ferroportin in the liver, enables the oxidation of Fe^{2+} to Fe^{3+} and facilitates its incorporation into transferrin. In WD, the loss of CP function results in iron accumulation in the liver, consequentlydecreasing circulating iron, thus causing anemia [26].

In the course of WD treatment, severe anemia and even pancytopenia may occur. An uncommon phenomena was reported as "copper deficiency anemia" by several case reports [27, 28], since copper chelators and zinc excess can cause copper deficiencyleading to a decrease in the trivalent iron [29]. A rare case reported [30] myelodysplastic syndrome mimicked by copper deficiency. Another explanation should also be considered as copper chelators such as DPA induce bone marrow suppression and autoimmune diseases [31]. Antos et al. described a drug-induced lupus erythematosus case caused by DPA after a year of treatment of WD [32]. By discontinuing DPA and methylprednisolone, the symptoms eventually disappeared. As autoimmunity maydestroy bone marrow, copper chelators may induce pancytopenia in an autoimmunological manner.

In addition to anemia, WD may be linked with pancytopenia by shortening TL. Recent literature provided studies on associations of metals with TL. Among common toxic metals, copper was negatively associated with TL in middle-aged and older Chinese adults [33]. Based on this concept, the question remains whether TL can be reversed when copper levels decrease. Our case demonstrated no recovery of TL after 6 months and 1 year of anti-copper therapy, suggesting either TL couldn't be reversed by copper level, or our testing interval was relatively short.

So far, there has not been reported any relations between TERT and copper metabolism or ATP7B mutations. However, there might be some genetic variations, in coding exons and non-coding variants, particularly in the TERT gene's intronic or intergenic regions, which could contribute to the patient's phenotype. A few studies reported pathogenic intronic variants or promoter in TERT to be a possible modifier of cancer risk [34, 35]. While our current data lack coverage in these regions, expanded genotyping of non-coding regions such as TERT promoter/enhancer regions or whole genome sequencing could provide additional insights.

Treatment for AA accompanied with WD

In our case, although copper metabolism was improved by copper chelation, BMF was not. Also failed to response to IST and stem cell stimulation, our patient finally recovered by allo-HSCT. Theoretically there are some complications in treating AA accompanied with WD. Because for one thing, copper chelator, especially D-penicillamine, is associated with bone marrow toxicity [36]; for another, during treatment in WD, symptomatic copper deficiency may occur

and present with hematologic symptoms, such as anemia and neutropenia [37]. These factors made AA more difficult torespond to stem cell stimulation, as reported in our case, allo-HSCT was the only reasonable management for AA accompanied with WD. Importantly, our patient remained under suspicion of having STS, and allo-HSCT is the only curative treatment [38]. Unfortunately, this patient still needs continuous surveillance because both STSs and oral cGVHD after allo-HSCT are at increased risk of developing malignancies [39].

Conclusions

The young patient with AA and WD responded well to allo-HSCT and copper chelators. Our case demonstrated no hematological improvement after anti-copper therapy, suggesting either no connections between AA and WD, or deeper underlying connections, since TL may play an essential role in leading to AA. Meanwhile, the mutation of TERT remained a possible initiating factor for the onset of AA.

Abbreviations

AA	Aplastic anemia
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
BMF	Bone marrow failure
cGVHD	chronic graft versus host disease
CP	Ceruloplasmin
DC	Dyskeratosis congenita
FA	Fanconi anemia
FISH	Fluorescence in situ hybridization
Hb	Hemoglobin
IST	Immunosuppressive therapy
MCV	Mean corpuscular volume
PLT	Platelet
PNH	Paroxysmal nocturnal hemoglobinuria
RBC	Red blood cell
Ret	Reticulocyte
STS	Short telomere syndrome
TERT	Telomerase reverse transcriptase (TERT)
TL	Telomere length
TPO	Thrombopoietin
WBC	White blood cell
WD	Wilson disease
WES	Whole-exome sequencing

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Author contributions Investigation and writing orginical draft, TC; methodology and review, JS; Investigation, LX, JC, XD; formal analysis, LL; data curation, JY and WL; supervision, ZS; validation, review and editing, RF. All authors reviewed the manuscript.

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Data availability Sequence data that support the findings of this study have been reserved https://doi.org/10.17632/m3kwttfnwc.1.

Declarations

Consent for publication All authors have reviewed the final version of the manuscript and consent to its publication in Annals of hematology.

Informed consent Written informed consent was obtained from all participants involved in the study for the use of their clinical data and images in the publication.

Competing interests The authors declare no competing interests.

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