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Case Report
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Aplastic Anaemia with RTEL1 Mutation Combined with Hepatocellular Adenoma: A Case Report and Literature Review

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Abstract

Aplastic Anaemia (AA) is a disease characterized by failure of the bone marrow. Androgens can be used to treat AA by controlling telomerase activity and promoting haematopoiesis in the bone marrow. Hepatocellular adenomas are benign tumours of the liver associated with the use of oral contraceptives and androgen therapy. Here, we report a case of aplastic anaemia patient with RTEL1 mutation and hepatocellular adenoma. The tumour reduced in size after embolisation, and it was resected because of rupture and haemorrhage. Androgens are used to treat AA, and some androgens can cause hepatocellular adenomas. Therefore, symptoms should be recognised early, and appropriate early treatment should be administered.

Keywords: Aplastic anaemia; Hepatocellular adenoma; Androgens; RTEL1

Case Presentation

A 14-year and 2-month-old male complained of skin petechiae for 15 days, pain in the mouth with pallor for five days, and epistaxis after admission in, May 2014. At the initial investigations, routine blood tests showed pancytopenia, examination of the bone marrow revealed a stimulated bone marrow image, pathological results demonstrated active proliferation of granulocytes and erythrocytes, and hypoplasia of megakaryocytes. Hepatitis B and C-related marker levels were normal. The fibrinogen level was mildly elevated, the bilirubin level was normal, Computed Tomography (CT) showed a slightly enlarged liver, and there were no obvious abnormalities in the rest of the abdomen. The patient was diagnosed with severe Aplastic Anaemia (AA) in May 2016 after bone marrow cytology and a biopsy showed a degree of hypoproliferation and a markedly reduced megakaryocyte count. Blood indices progressively deteriorated during follow-up (Table 1) and there were no megakaryocytes or hypoproliferative nucleated cells in the bone marrow. InMay 2016, the patient commenced oral cyclosporine and stanozolol, with intermittent iron removal therapy. Due to economic constraints, the combined treatment of anti-thymocyte globulin and cyclosporine was not pursued. During this period, treatment was discontinued because of hypertension, renal impairment, gingival hyperplasia, or infection, and the patient was subsequently switched to oral tacrolimus for three months. The patient's parents refused permission to perform genetic tests related to failure of the bone marrow, thus the patient continued to be treated with oral medication.

In August 2022, the patient presented with intolerable left lower thoraco-abdominal pain and left shoulder pain. His bilirubin level was normal, the albumin level was decreased, the transaminase level was increased, and the time to activate partial thromboplastin was decreased. Abdominal ultrasonography revealed a slightly enlarged liver with multiple substantial lesions; CT scan enhancement revealed multiple space-occupying lesions in the liver. The liver was slightly plump due to a cause yet to be determined, as infections, neoplasms, or tumor-like lesions could not be excluded. Liver puncture biopsy yielded a limited tissue sample, which revealed some areas of dilated hepatic blood sinusoids, congestion and hepatocyte iron deposition. There were focal hepatocytes with mild to moderate heterogeneity, scattered β-catenin positive nuclei, hepatic adenomas were excluded, and *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were identified. A diagnosis of β-catenin activated hepatocellular adenoma was considered. During follow-up, abdominal ultrasonography and CT showed that the intrahepatic space continued to grow with possible haemorrhage.

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Table 1: Blood routine of the patient. May 2014 is the time of initial diagnosis, May 2016 is the time of confirmation, and August 2022 is the time of onset of abdominal pain.

Date	Leukocyte (10^9/L)	Platelet 10^9/L)	Erythrocytes (10^{12}/L)	Hemoglobins (g/L)	Neutrophil (10^9/L)	Reticulocyte (10^{12}/L)
In May 2014	3.87	31	2.74	89	1.35	0.008
In May 2016	2.38	17	1.82	65	0.52	0.013
In August 2022	3.04	2	1.48	51	0.82	0.04
Minimum	2	0	1.04	27	0.13	0.008
Recent	1.44	24	2.29	66	0.22	0.01

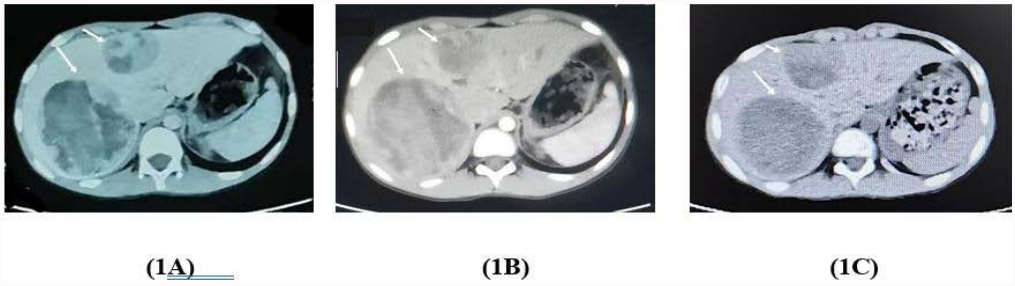

Figure 1: CT images. A(five days before artery embolization): slightly low-density rounded and flaky shadows of varying densities, with clear borders, and the largest one was in the right posterior lobe of the liver, measuring about 96.2 mm × 80.6 mm; B(five days before artery embolization): patchy flocculent enhancement was seen in the arterial phase after enhancement; C(ten days after artery embolization): as lightly low-density shadow with a clear boundary, and in the right posterior lobe of the liver was the largest one, with the size of about 77.2 mm × 74.2 mm.

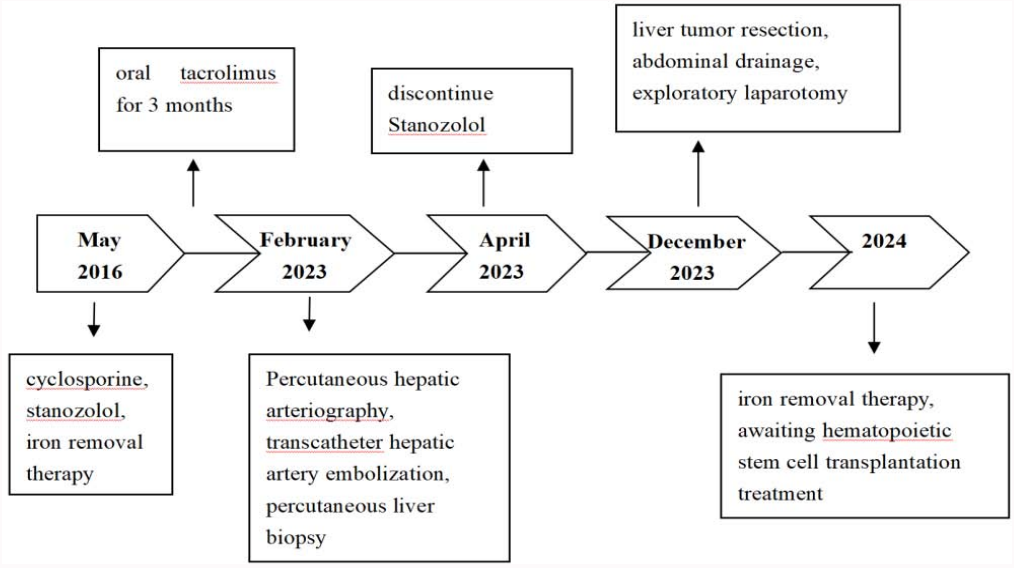

Figure 2: Summary of the treatment process.

In February 2023, the patient underwent percutaneous hepatic arteriography, transcatheter hepatic artery embolisation, percutaneous liver biopsy, and other treatments. The specific CT scan enhancement images are shown in Figure 1. Considering the presence of hepatic lesions combined with infection, stanozolol was discontinued in April 2023. The effect of oral medication and blood transfusion was poor, and telomere length was 6.81 kb, which is very short for a 13-year-old, while a bone marrow exhaustion gene test showed a telomere length regulator enzyme 1 (*RTEL1*) mutation, which was a paternal heterozygous mutation. In December 2023, the liver tumour was resected due to rupture and haemorrhage. A post-surgery biopsy revealed iron deposition in some hepatocytes, mild-to-moderate atypia in focal hepatocytes, diffuse glutamine synthetase positivity, and scattered β-catenin positive nuclei. One week after surgery, the patient resumed a semi-liquid diet without experiencing abdominal pain or distension, and there were no symptoms of nausea or vomiting. Two weeks after surgery, abdominal colour Doppler ultrasound showed an abnormal hypoechoic area in the posterior lobe of the liver without an obvious blood supply. Four months postoperatively, an abdominal colour ultrasound review revealed small low-echo nodules in the liver with a visible blood supply, but due to the small size clinical intervention was not deemed necessary. Currently, the patient has ceased cyclosporine therapy because of a poor therapeutic effect and undergoing intermittent iron chelation therapy, while awaiting haematopoietic stem cell transplantation. There was no recurrence of liver lesions. The treatment regarding this

patient is summarised in Figure 2.

Discussion

Aplastic anaemia is a disease characterized by failure of the bone marrow. Androgens, such as stanozolol and danazol, are commonly used in combination with immunosuppressive therapy for patients with AA [1]. Androgens stimulate the production of erythropoietin, upregulate the expression of erythropoietin receptors, elevate the erythrocyte level, and upregulate the expression of telomerase reverse transcriptase genes and the activity of telomerase in lymphocytes and CD34+ haematopoietic stem cells *in vivo* [2]. Hyperphysiological doses and prolonged use of androgens affects multiple organs, leading to cardiovascular, neurological, endocrine, gastrointestinal, renal, and haematological disorders. The pathogenesis is currently thought to include disturbances in antioxidant factors, increased bile acid synthesis, and increased induction of hepatocyte proliferation [3]. In earlier studies, some patients were reported to have died due to severe liver disease and jaundice, but it was not clear if complications such as viral hepatitis and iron overload were due to the disease [4]. The RTEL1 gene encodes a DNA helicase that is important for telomere maintenance and genomic stability [3]. This gene regulates telomere length, and mutations result in a compromised telomere length, which in turn leads to the development of disease. Mutations in genes encoding telomerase components have been associated with some lung, skin, bone marrow, and liver diseases. Mutations in the RTEL1 gene are often present in patients with gliomas [5] and can be found in interstitial lung disease, bone marrow failure diseases, myeloid tumours, cirrhosis, and hepatocellular carcinomas [3]. In bone marrow failure diseases, Dyskeratosis Congenita (DC) is a telomere disorder characterised by a diagnostic triad of abnormal skin pigmentation, dysplastic nails, and oral leukoplakia [6]. This disease is mainly inherited by X-linked recessive inheritance, but some are inherited by autosomal dominant or autosomal recessive inheritance. Therefore, there are significantly more males with DC [7]. The RTEL1 gene mutation has been proven to be a pathogenic mutation [8], with autosomal dominant and autosomal recessive genetic pathways [9]. Hepatic disturbances have been reported in 7% of patients with DC and the liver has heterogeneous histopathological manifestations, including non-cirrhotic portal hypertension, intrahepatic shunting and angiosarcoma [10]. In a mouse liver cancer model, the mutation presented as an overexpression similar to that of the proto-oncogene, causing gene amplification, and the mechanism may involve a large number of tumour cell mitoses and the formation of multinucleated cells. However, this study was experimental, thus lacking clinical evidence. Therefore, further studies are required [5]. The development of cirrhosis and hepatocellular carcinoma in patients with AA is closely associated with telomerase abnormalities [11]. In patients with AA, androgens can restore bone marrow haematopoiesis by elevating telomerase activity and repairing depleted telomeres but patients are susceptible to hepatotoxicity and muscle cramping [12].

Hepatocellular Adenoma (HCA) is a rare, benign liver disease that mainly occurs with the use of oral contraceptives and androgen therapy. Patients with HCA may be asymptomatic, presenting only with right upper abdominal distension and pain, or may present with acute abdominal shock due to rupture of the tumor and haemorrhage [13]. HCA can be classified as inflammatory, hepatocyte nuclear Factor 1α mutant, β-catenin activated, or an undetermined subtype and carries the risk of haemorrhage, rupture, and potential malignancy. The risk of malignancy is based on whether there was prolonged use of androgens or due to other potentially higher risk factors, such as type I glycogen storage disease, β-catenin activated type, and male sex. In paediatric patients, β-catenin activated tumours appear to be the predominant subtype [14]. Androgen exposure and short telomere length are risk factors for HCA in patients with AA [15]. The androgen receptor signaling pathway can induce the development of liver cancer through various mechanisms [16]. However, the mechanism of action of androgens on HCA remains unclear. Compared to normal liver tissue, the expression of androgen receptors is increased in HCA, and these receptors mediate the action of androgens on the tumour or adjacent liver parenchyma, which may promote the growth of the tumour [17].

Imaging plays an important role in the characterization and treatment of HCA and can improve the diagnosis of different subtypes. Magnetic Resonance Imaging (MRI) is superior to other imaging methods for diagnosing HCA, and the diagnosis of androgen-associated HCA can be based on histopathological examination [18]. The median time from androgen use to the progression to HCA was 13 years, and for patients with AA, the shortest period was six years [19]. In this case, the patient was male, pain in the left lower abdomen was the first symptom, combined with a seven-year history of androgen usage and the results of puncture biopsy, β-catenin activated adenoma was diagnosed, and seven years had elapsed after treatment with stanozolol until the diagnosis. The patient had an RTEL1 mutation and a very short telomere length, which are high-risk factors for the development of liver disease and affect prognosis. However, the RTEL1 gene test result in this patient was uncertain, and his father had no related clinical manifestations; therefore, DC could not be diagnosed. Owing to the short follow-up time, the patient is currently awaiting haematopoietic stem cell transplantation, and the subsequent efficacy evaluation cannot be performed.

Treatment of HCA mainly includes surgical resection, transarterial embolisation, and radiofrequency ablation. Transarterial embolisation effectively reduces the occupancy of masses; however, the risk of malignant transformation remains unknown [20]. Most female patients with HCA can be treated conservatively; their liver function can normalise and the mass can regress after hormone withdrawal [21]. For patients with HCA >5 cm in diameter or growing in size, early surgery not only removes the tumour but also eliminates the risk of tumour progression [22]. The current patient underwent transcatheter hepatic artery embolisation, followed by resection of the tumour due to rupture and haemorrhage. No obvious signs of haemorrhage were found in the postoperative review. Early recognition of HCA is particularly important in patients with AA receiving long-term androgen therapy. Screening for hepatitis B, hepatitis C, ferritin, and complete liver ultrasonography should be performed at the beginning of the disease, every six months thereafter, and then annually. To avoid progression to hepatocellular carcinoma, patients should not be prescribed other hepatotoxic drugs [4]; drug doses should be adjusted or even discontinued, if necessary. It is also necessary to monitor liver function every 2-3 months, and MRI should be actively refined [15]. Abdominal ultrasound should be repeated regularly after any treatment to monitor for malignant transformation of the tumour.

In conclusion, androgens promote haematopoiesis and are commonly used to treat acquired and congenital AA. However, hyperphysiological doses and prolonged use of androgens may cause disorders in various body systems, particularly hepatotoxicity, which

may lead to HCA. Long-term androgen-exposed patients with AA and a short telomere length are more prone to HCA. The RTEL1 gene is involved in the regulation of telomere length, which is also related to the manifestation of HCA. Therefore, additional attention should be paid to patients with AA who continuously receive androgens. The liver function of these patients should be regularly monitored, and relevant examinations should be promptly performed so that HCA can be recognised at an early stage, and a treatment plan can be formulated on an individual basis.

Author Contributions

Gao Jingchen wrote the manuscript. Liu Haiyan, Yang Hui, Feng Ye, Qin Jiebin,Wen Xianhao managed the patients' care. Wen Xianhao revised the manuscript. All the authors read and approved the final manuscript.

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Conflict of Interest Statement

The remaining authors declare no conflict of interests.

Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The study was approved by the ethics committee of Children's Hospital of Chongqing Medical University.

Consent for Publication

Written informed consent was obtained from the patient to have the case details and any accompanying images published.

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