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Pomalidomide successfully treated transfusion-dependent epistaxis in hereditary hemorrhagic telangiectasia: a case report

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Case Report

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Abstract

Hereditary hemorrhagic telangiectasia (HHT, Osler disease) is an inherited vascular disorder characterized by recurrent bleeding from fragile telangiectatic vessels. Epistaxis is the most common manifestation and often results in chronic transfusion-dependent anemia. Although anti-angiogenic therapies have shown clinical benefit, effective oral treatment options remain limited. We report a 75-year-old man with HHT and transfusion-dependent epistaxis who experienced a remarkable response to pomalidomide. He had concomitant smoldering multiple myeloma with an IgG-κ monoclonal protein and received thalidomide for hematological disease without improvement of epistaxis. Because of the limited efficacy of thalidomide, treatment was switched to pomalidomide (2 mg/day). After three weeks of therapy, epistaxis markedly decreased and red blood cell transfusions were no longer required. Pomalidomide was temporarily discontinued because of worsening pleural effusion, which was subsequently attributed to heart failure. During treatment interruption, epistaxis gradually recurred, leading to renewed transfusion dependence. Reintroduction of pomalidomide again resulted in rapid improvement of epistaxis and sustained transfusion independence without recurrence of pleural effusion. This clinical course strongly suggests a therapeutic effect of pomalidomide on HHT-associated bleeding. Pomalidomide may represent a promising oral therapeutic option for patients with severe transfusion-dependent HHT, particularly when conventional treatments are insufficient.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler disease, or Osler-Weber-Rendu disease, is an autosomal dominant vascular disorder caused primarily by pathogenic variants in *ENG*, *ACVRL1* or *SMAD4* [1]. Defective transforming growth factor-β/bone morphogenetic protein signaling results in abnormal vascular remodeling and fragile telangiectatic vessels, leading to recurrent bleeding [1–3]. Epistaxis occurs in more than 90% of affected patients and often causes chronic iron deficiency anemia or transfusion dependence [2].

Management of HHT-associated epistaxis includes local procedures, antifibrinolytic agents, anti-angiogenic therapy, and systemic agents; however, many patients remain refractory to available treatments [2]. Immunomodulatory drugs (IMiDs), particularly thalidomide, have been reported to reduce bleeding by promoting vascular maturation and inhibiting pathological angiogenesis [4]. Nevertheless, long-term administration of thalidomide is frequently limited by peripheral neuropathy, constipation, and thromboembolic complications.

Pomalidomide is a third-generation IMiD with potent immunomodulatory and anti-angiogenic properties and a more favorable toxicity profile than thalidomide [4]. The PATH-HHT trial recently demonstrated that pomalidomide significantly reduced epistaxis severity and improved quality of life in patients with moderate-to-severe HHT-associated epistaxis [6–8]. However, reports describing successful withdrawal from chronic transfusion support remain scarce. We report a patient with HHT and concomitant

smoldering multiple myeloma whose transfusion-dependent epistaxis dramatically improved after initiation of pomalidomide, recurred during drug withdrawal, and responded again after rechallenge.

Case report

A 75-year-old man was referred to our institution for evaluation of chronic transfusion-dependent anemia secondary to recurrent epistaxis. He had experienced recurrent spontaneous epistaxis since his 40s. Physical examination revealed multiple telangiectatic lesions involving the lower extremities, fingers, lower lip, and right cheek (Fig. 1). There was no family history of HHT.

Contrast-enhanced computed tomography and magnetic resonance imaging showed no evidence of pulmonary, cerebral, or hepatic arteriovenous malformations. According to the Curaçao diagnostic criteria, the patient fulfilled two criteria (recurrent epistaxis and mucocutaneous telangiectasia), consistent with possible HHT. Genetic testing identified a heterozygous germline *ACVRL1* (p.Arg374Trp) pathogenic variant, establishing the molecular diagnosis of HHT [1].

During evaluation for monoclonal gammopathy, serum immunofixation revealed an IgG-κ monoclonal protein. Bone marrow examination demonstrated 20.4% clonal plasma cells without myeloma-defining events, including osteolytic lesions, hypercalcemia, renal dysfunction attributable to plasma cell disease, or symptomatic anemia. He was therefore diagnosed with smoldering multiple myeloma. Thalidomide therapy was initiated on April 4, X (IgG 4810 mg/dL, Epistaxis Severity Score;ESS 8.08). Despite continued treatment, severe epistaxis persisted, and weekly red blood cell transfusions remained necessary.

Because of poor efficacy of thalidomide (100 mg/day), treatment was switched to pomalidomide at 2 mg/day on March 27, X + 1. After approximately three weeks, epistaxis markedly decreased, hemoglobin levels gradually improved, and transfusion support was no longer required. However, increasing pleural effusion developed, and pomalidomide was temporarily discontinued because a drug-related adverse event could not initially be excluded. Subsequent evaluation suggested that the pleural effusion was secondary to congestive heart failure due to severe iron deficiency anemia, and the effusion resolved with diuretic therapy.

Approximately nine weeks after discontinuation of pomalidomide, epistaxis progressively worsened, leading to recurrent transfusion dependence. Given the favorable response before treatment interruption and the absence of evidence implicating pomalidomide in the pleural effusion, pomalidomide at 2 mg/day was restarted on July 3, X + 1. Epistaxis again improved rapidly (ESS 3.44 on July 31, X + 1), and the patient achieved sustained transfusion independence without recurrence of pleural effusion (Fig. 2).

Discussion

This case demonstrates that pomalidomide can effectively control severe transfusion-dependent HHT-associated epistaxis. The remarkable clinical response observed in our patient further supports the

potential role of IMiDs as systemic therapy for refractory HHT-associated bleeding.

Abnormal angiogenesis and defective vascular maturation are central features of HHT pathogenesis [1–3]. IMiDs have been shown to enhance pericyte recruitment, stabilize immature blood vessels, and suppress pathological angiogenesis [4]. In a landmark experimental study, Lebrin et al. demonstrated that thalidomide increased platelet-derived growth factor-B (PDGF-B) expression, improved pericyte coverage, and reduced bleeding in both murine models and patients with HHT [4]. These findings provide a biological rationale for the use of IMiDs in HHT-associated bleeding.

Several case reports had also demonstrated successful control of severe HHT-associated bleeding with anti-angiogenic therapies (Table 1.), including thalidomide, bevacizumab, and pazopanib [4–9]. In particular, thalidomide was shown to reduce recurrent epistaxis by promoting vascular maturation, while bevacizumab and pazopanib have been reported to improve refractory HHT-associated epistaxis and reduce transfusion requirements in individual patients with transfusion-dependent bleeding [4–9].

Unfortunately, thalidomide failed to improve epistaxis in the present patient, whereas pomalidomide produced a dramatic clinical response. Although the precise mechanism remains unclear, pomalidomide has greater affinity for cereblon and more potent downstream immunomodulatory activity than thalidomide while generally exhibiting a more favorable toxicity profile [10]. These pharmacological differences may translate into more effective vascular stabilization in selected patients with HHT, although this hypothesis requires further investigation.

The recently published PATH-HHT trial, a randomized, placebo-controlled phase 3 study, demonstrated that pomalidomide significantly improved the ESS (especially nose bleeding), with a mean reduction of 1.84 points from baseline compared with 0.89 points in the placebo group (between-group difference, -0.94 points; $P = 0.004$) [11]. Pomalidomide also improved health-related quality of life and reduced transfusion requirements in patients with HHT-associated epistaxis [11–13]. An exploratory subgroup analysis suggested that patients with *ACVRL1* variants derived less clinical benefit than those with *ENG* variants. Nevertheless, despite harboring a germline *ACVRL1* pathogenic variant, our patient experienced a marked reduction in epistaxis and complete withdrawal from chronic red blood cell transfusion [13]. This finding suggests that *ACVRL1* genotype alone should not preclude the use of pomalidomide and that additional genetic or biological factors may influence treatment responsiveness.

Another important feature of our case is the clear dechallenge–rechallenge response. Epistaxis markedly improved after initiation of pomalidomide, recurred during treatment interruption, and improved again following reintroduction without recurrence of pleural effusion. This temporal relationship provides compelling evidence for a causal effect of pomalidomide on HHT-associated bleeding. To our knowledge, this is among the first published case reports documenting a dechallenge–rechallenge response to pomalidomide in HHT, thereby providing additional real-world evidence supporting its clinical efficacy.

In conclusion, pomalidomide may represent an effective oral therapeutic option for patients with severe transfusion-dependent HHT-associated epistaxis. Further prospective studies are warranted to determine its optimal dosage, treatment duration, long-term safety, and position within current therapeutic algorithms [14, 15].

Declarations

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Author contributions

YO wrote the manuscript. YO, TS, and TT were involved in the clinical management of the patient. MK supervised this study. All authors have given their final approval of the manuscript.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Thalidomide and pomalidomide were administered as treatment for the patient's smoldering multiple myeloma and not specifically for hereditary hemorrhagic telangiectasia (HHT). The marked improvement in HHT-associated epistaxis was an unexpected clinical observation during the course of treatment. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patient consent for publication

Informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare no conflicts of interest.

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Table

Table 1 is available in the Supplementary Files section.

Figures

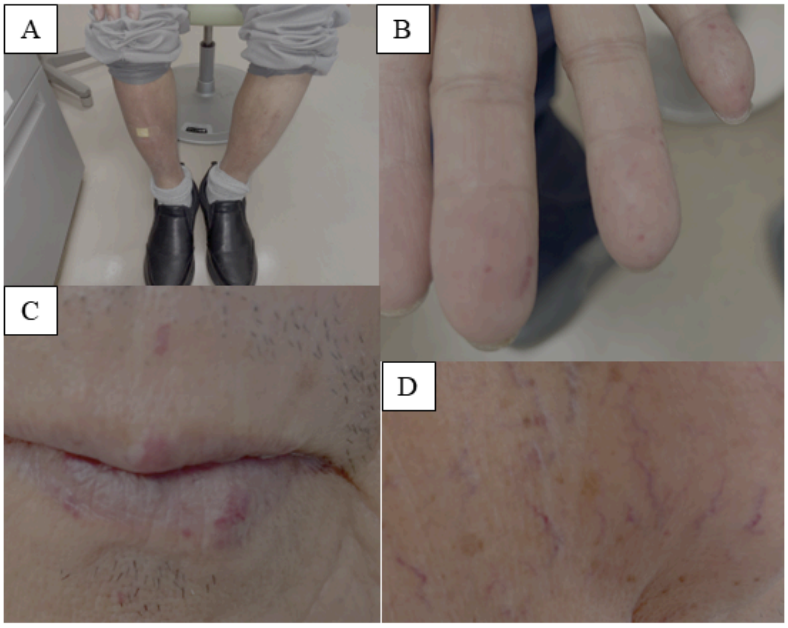

Fig. 1 Multiple telangiectatic lesions.
(A)lower extremities, (B)fingers, (C)lower lip, (D)right cheek.

Figure 1

See image above for figure legend.

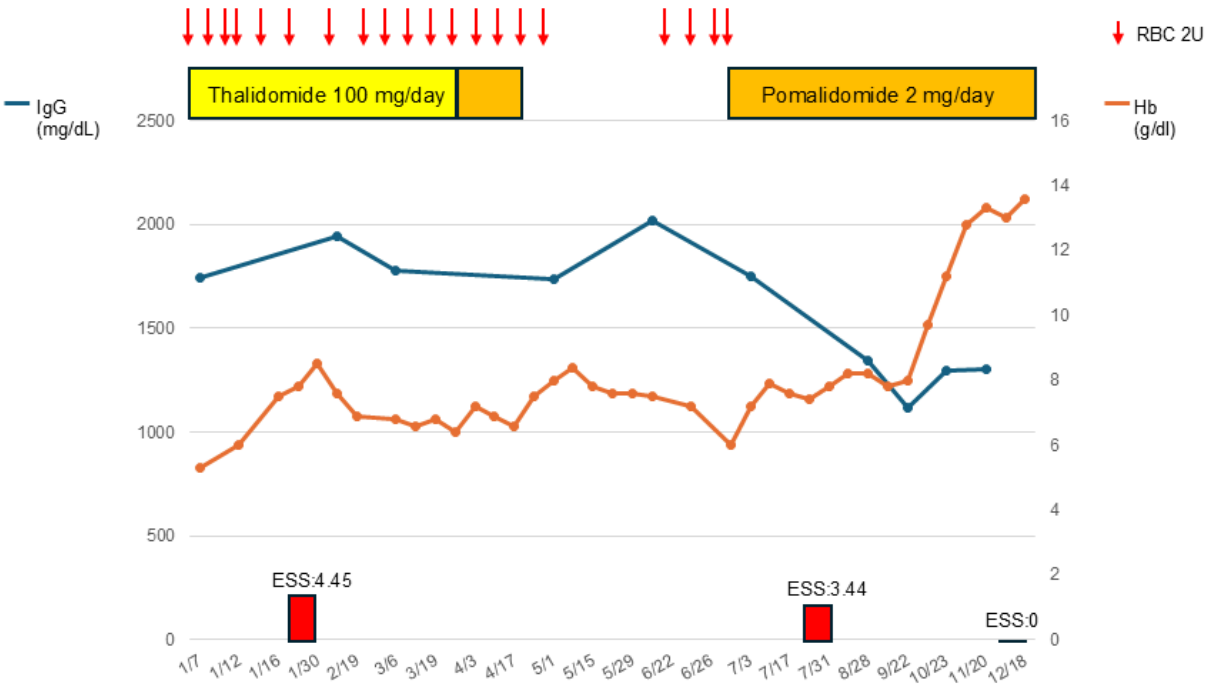

Fig.2 Dynamics of IgG and hemoglobin levels. *Abbreviations*: IgG:Immunoglobulin G, Hb:Hemoglobin, RBC:Red cell concentrate, ESS:Epistaxis Severity Score

Figure 2

See image above for figure legend.

Supplementary Files

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- Table1..xlsx