Key words
Candidemia, hematologic malignancy, neutropenia, Candida krusei, fluconazole.

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β-thalassemia intermedia resulting from compound heterozygosity for an IVSI-1 (G-A) and a silent 5' UTR +33 (C-G) mutation

A Caucasian woman from Plasencia, Spain, was found to have a thalassemia intermedia phenotype due to a double heterozygosity for a IVSI-1 (G-A) mutation and a silent 5'UTR +33 (C-G) mutation. This silent mutation has been described previously, but with a different haplotype, in two unrelated Greek Cypriot families.

Sir,

A Caucasian woman from Plasencia, Spain was found to have a thalassemia intermedia phenotype.

Table 1. Hematologic data and Hb analysis.

Subject	Propositus		Father	Mother
	Pre S	Post S		
Hb (g/dL)	6.8	8.2	10.1	13
MCV (fL)	61.4	63	66	84
MCH (pg)	19.7	20	21	28
Ferritin (ng/mL)	237	614	n.d.	n.d.
Hb A2 (%)	5.8	4.1	5.0	3.0
Hb F (%)	n.d.	3.2	1.2	0.3
IEF	AA2F	AA2F	AA2	AA2

HbA_2 assayed by column chromatography and HbF by alkali denaturation. IEF using precasting gels (Pharmacia) of agarose pH 6–8. Pre-S – pre splenectomy; Post-S – post splenectomy.

Her father had β-thalassemia (β-thal) minor and her mother had normal hematologic indices. We found that the woman had inherited an IVSI-1 (G-A) mutation from her father and a silent 5'UTR +33 (C-G) mutation from her mother.

A few mutations have been described in the β-globin gene, most frequently in the promoter or in the 5' untranslated regions, leading to a slight decrease of β-globin chain synthesis.[1]

Carriers of these silent mutations show normal or slightly decreased hematologic parameters and a normal or slightly elevated Hb A_2 level; the co-inheritance of another β thalassemia mutation in *trans* gives rise to a thalassemia intermedia phenotype. Silent thalassemia mutations are most often identified among thalassemia intermedia patients who have one parent with a normal phenotype.[2]

The propositus was 49 years old. She had thalassemic facies, jaundice, hypochromic microcytic

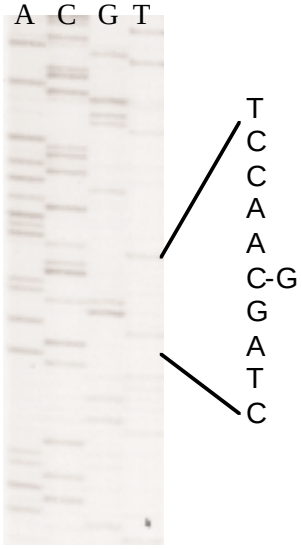

Figure 1. Sequencing of the proband's DNA fragment showing the +33 C-G mutation.

anemia, and had been splenectomized at the age of 48 with clinical improvement and an increase in hemoglobin level (Table 1). Before splenectomy she had required occasional transfusion therapy.

Her father and sister had the typical hematologic features of β-thalassemia minor whereas her mother had normal red cell indices with a borderline Hb A_2 level (Table 1) and no α-globin gene triplication.[3]

Direct sequencing[4] of the propositus' β-globin gene showed compound heterozygosity for the Mediterranean β IVSI-1 (G-A) mutation and for a recently described 5' UTR +33 C-G mutation (Figure 1). These mutations were confirmed respectively by *BsaB* I and *Nla* IV amplified DNA digests. The IVSI-1 (G-A) mutation is present in her father's and sister's β-globin gene and the 5' UTR +33 (C-G) mutation is present in her mother's β-globin gene.

The C to G mutation in the +33 position of the β-globin gene was first described in two unrelated Greek Cypriot families[5] associated with β haplotype II (– + + – + + +) according to Orkin.[6] In the present case the 5' UTR +33 (C-G) mutation is associated with β haplotype V (+ – – – – + –) suggesting an independent origin for the mutation in this family.

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Peri-operative use of recombinant human erythropoietin in Jehovah's Witnesses

The care of Jehovah's Witnesses who refuse blood transfusion on religious grounds is a continuing clinical challenge. Options for treating these patients are limited. We present the cases of four Jehovah's witnesses (2 males, 2 females, mean age 54.7 years) who successfully underwent total hip arthroplasties (one of them twice) with peri-operative rHuEpo support.

Sir,

Four patients refused allogeneic and autologous blood transfusion based on religious convictions. The patients' hematologic data are shown in Table 1. We administered rHuEpo pre-operatively to a total dose of 10,000 IU (not corrected for body weight), three times weekly subcutaneously, thirty days prior to operation in order to achieve a Hb ≥14 g/dL. Administration was continued for another thirty days after surgery in order to avoid cardiopulmonary complications due to low Hb levels. Ferrous sulfate (300 mg) was also administered *per os* daily. Complete blood counts, erythropoietin levels and ferritin levels were monitored throughout the study period and the values at the initiation of rHuEpo administration, on the day of the operation and at the end of the therapy are presented in Table 1.

Five total hip arthroplasties (onr patient had two operations) were performed successfully, without any blood transfusion and no complication due to excessive blood loss or low Hb levels were noted. Hb levels after a 30-day rHuEpo administration were significantly increased (Table 2). A significant increase was also noted in erythropoietin (epo) levels (Table 2). No significant changes were noted in either ferritin levels or the number of white blood cells and platelets.

rHuEpo administration was well tolerated. No change was observed in the patients' blood pressure, renal and hepatic function were within normal ranges and there was no evidence of deep venous thrombosis in the postoperative period.

Patient #1 underwent two operations. After the second one she presented with severe melena due to an acute stress ulcer. Although her Hb value was less than 4.5 g/dL she repeatedly refused a blood transfusion and was transferred to the intensive care unit for supportive therapy, where she was only administered rHuEpo and iron supplements on a daily basis. After two months her Hb value had increased up to 10 g/dL and she was discharged in an excellent condition.

The refusal of Jehovah's Witnesses to accept transfusions has accelerated the administration of rHuEpo in the perioperative setting, especially in joint replacements[1,2] because of the elective nature of these operations. Although thrombotic events complicate rHuEpo treatment in renal failure, in a recent integrated analysis by de Andrade *et al.*,[3] rHuEpo administered in elective orthopedic surgery patients was not identified as a risk factor for thrombotic/vascular events. In addition, in a multicenter, double–blind, placebo-controlled study[4] the incidence of deep vein