

**Case Report**



SOI: <http://s-o-i.org/1.15/ijarbs-2-12-35>

**Aggravation of Iron Deficiency Anemia after Hormone Replacement Therapy in a Patient with Hypopituitarism and Hepatosplenomegaly**

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**Abstract**

Iron deficiency anemia (IDA) is a common worldwide hematological disorder that is more apparent in children, teenagers and the elderly. The cornerstone of proper management of IDA is identification and treatment of the underlying etiology of ID. Here we reported an eighteen years old female patient with a triad of severe IDA, mild hepatosplenomegaly and hypopituitarism. Her IDA was refractory to erythropoietin, iron supplementation and vitamin C treatments, intriguingly her anemia worsen further after adding hormone replacement therapy. This case study highlighted the importance to specify IDA, hepatosplenomegaly and hypopituitarism as a distinguished syndrome. Furthermore it urged the need for future research to find out the exact pathophysiologic link between IDA and hypopituitarism in order to establish a proper management strategy for such cases. Also this case study directed physicians and hematologists to consider hormonal assay in patients with refractory anemia.

**Keywords:** Iron deficiency anemia, panhypopituitarism, hormonal replacement.

**Introduction**

Iron deficiency anemia is the most common type of anemia particularly in developing countries (WHO, 2008). Numerous etiologies have been listed in medical textbooks that can lead to either ID and/or IDA, the most prevalent causes were abnormal uterine bleeding in females and gastrointestinal bleeding in males (Vranken, 2010; Goddard et al., 2011; Liu and Kaffes, 2012). Although the association between panhypopituitarism and anemia is documented in many researches (Gokalp et al., 2009), however panhypopituitarism is not included in the long list of causes of IDA. This may be because the exact pathophysiologic mechanism of ID in patients with panhypopituitarism is still unclear. This case study discussed the case of a female patient presented with a triad of IDA, mild hepatosplenomegaly and hypopituitarism. Her IDA deteriorated with the addition of hormone replacement therapy.

**Case presentation**

An eighteen years old female patient was presented, on April 2011, at the outpatient clinic of Hematology and BMT unit of Internal Medicine Department, Assiut University Hospital (AUH). She lived in an urban region in Assiut Governorate Egypt; she was a student, unmarried and had no special habits. Her complaints were headache, dizziness, generalized malaise, and fatigue. Her menstrual history denoted primary amenorrhea.

On examination severe pallor, oral fissures, and pale conjunctivae were detected, however patient was hemodynamically stable. Small, discrete, mobile, non tender circular and longitudinal cervical lymph nodes were also palpable, also mild hepatosplenomegaly was detected.

Anthropometric measures and assessment showed that her body mass index is at the lower limit of normal

(18.5 kg/m<sup>2</sup>). Furthermore patient had underdeveloped secondary sexual characters in the form of atrophic breasts, scanty axillary and pubic hair. Her ophthalmic assessment revealed no visual field defects.

Patient was admitted at Hematology and BMT unit, AUH, and fully investigated. Her laboratory test results are presented in table 1, these included complete blood count (CBC) and blood smear, serum iron (S. Fe) and total iron binding capacity (TIBC),

stool and urine analyses, kidney and liver function tests, co-agulation profile, serum Na<sup>+</sup> and k<sup>+</sup>, and hormonal assay. Her peripheral hemogram revealed severe microcytic hypochromic anemia, moreover her iron studies showed low serum iron and raised total iron binding capacity proving her anemia to be iron deficient. Nevertheless the underlying etiology of her IDA was obscure. Expectedly her hormonal profile showed hypopituitarism and her electrolytes revealed mild hyponatremia and hypokalemia.

**Table 1 Laboratory test of blood, stool and Samples**

Laboratory test	Patient's results	Reference range*
<b>CBC</b>		
WBCs (10 <sup>3</sup> /ul)	8.3	4-11
RBCs (10 <sup>6</sup> /ul)	2.5	4.0-5.2
Hb (g/dl)	5	12-14
MCV (fl)	53	80-100
MCH (pg)	25.3	28-32
MCHC(g/dl)	24	32-36
Hct (%)	29	36-47
RDW (%)	17	11.5-14.5
Retic.(%)	0.3	0.5- 1.5%
Plt. (×10 <sup>3</sup> /μl)	540	150-450
<b>Blood film</b>	Microcytosis with hypochromia, thrombocytosis, normal WBCs and tear drops	
<b>Stool analysis</b>		
Parasites	Negative	
Occult blood	Negative	
<b>Sickling test</b>	Negative	
<b>Hemoglobin electrophoresis</b>	Type A hemoglobin	
LFT	Normal	
KFT	Normal	
PT	Normal	
PC	Normal	
INR	Normal	
<b>Electrolytes</b>		
S. Na+( mmol/L)	132	135-145
S. K++( mmol/L)	3.2	3.5-5.5

\*(Armbruster et al., 2007), LFT= liver function tests, KFT= kidney function tests, PT= prothrombin time, PC= prothrombin concentration, INR= international normalized ratio

Patient was radiologically assessed with plain x-ray hands and skull, abdominal and pelvic ultrasound, and MRI skull. The x-ray skull together with clinical history diagnosed the case most probably post-traumatic hypopituitarism (PTH). The abdominal ultrasound ensured the clinically detected mild hepatosplenomegaly, and the MRI head re-affirmed PTH.

There was neither similar condition nor endocrine or metabolic disease in her family.

She was started on oral iron therapy (200 mg/day) and vitamin C, and subcutaneous injection of recombinant human erythropoietin ((Recormon 500 IU (corresponding to 4.15 micrograms epoetin beta) /0.3 mL) 3 times weekly.

Recormon was administered by a hematologist and after excluding possibility of anaphylaxis. Also, patient was referred to an endocrinologist who prescribed hormone replacement therapy (HRT) in the form of prednisone (15mg/day PO in divided doses), L-thyroxine (50 mcg PO/day), and estrogen (0.3-0.625 mg PO once daily in cyclic regimen (3 weeks on, 1 week off)). However, patient did not receive growth hormone replacement therapy.

Patient was discharged after 17-days on treatment for both IDA and hypopituitarism and was instructed for regular follow up at the outpatient clinic after 15-days. However, patient came back after one month with

similar symptoms and signs of her first presentation but more severe. Patient was re-admitted and re-assessed. Detailed medical history was taken, stressing on patient adherence to her medications, it showed adherence to treatment. Results of her laboratory investigations on her second visit showed normalization of her hormonal and electrolyte profile, meanwhile aggravation of her IDA was obvious, and figure 1 showed her hormonal profile on admission and after 1-month of treatment. Patient received a unit of packed RBCs and growth hormone (GHT) was added to her treatment at a dose of 0.04 mg/kg/week SC, that was increased after 4-weeks to 0.05 mg/kg/week.

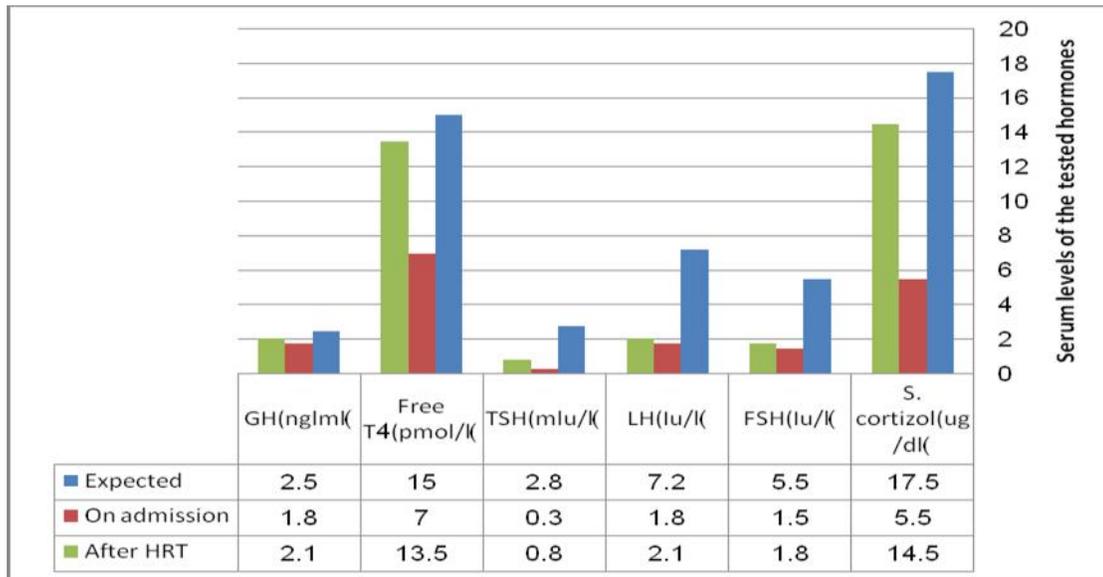


Figure 1. Hormonal profile of the patient on admission and after 1-month of hormone replacement therapy (HRT).

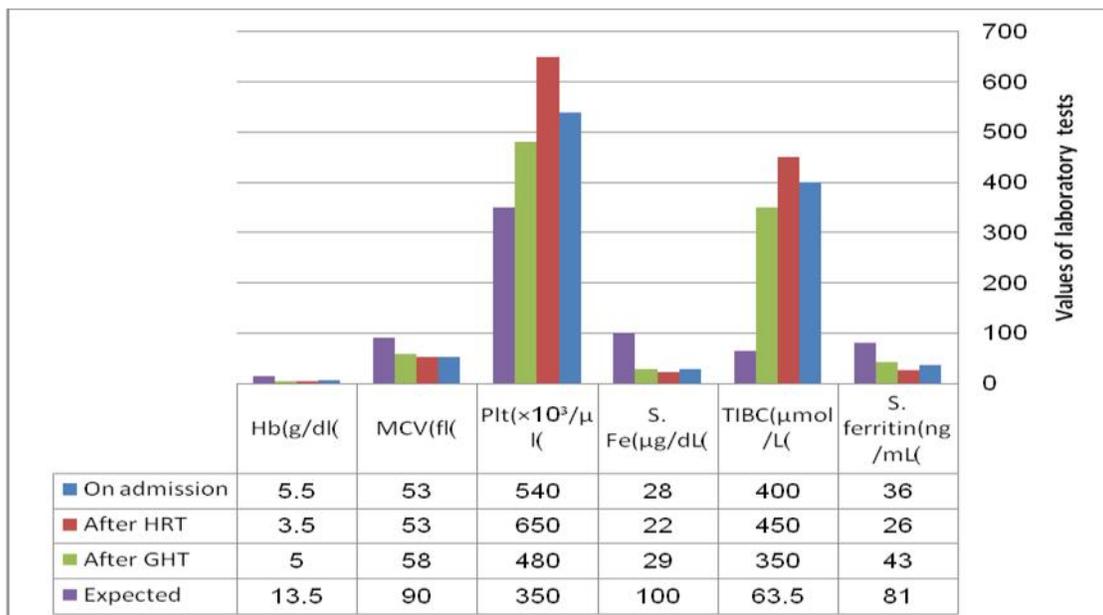


Figure 2. Hematologic and iron studies of the patient on admission, after HRT and GHT.

Regular follow up of the patient at the hematology outpatient clinic showed gradual progressive increment of her blood hemoglobin, MCV, serum iron and ferritin. On the contrary her platelet count and TIBC were obviously reduced, and figure 2 showed patient's hematologic and iron studies on admission, after HRT and GHT.

## Discussion

The association between panhypopituitarism and anemia was reported, where normocytic normochromic anemia was found to be not uncommon in patients with Simmond's disease (*Kreitschmann-Andermahr, 2007*). This could be explained by the fact that certain pituitary dependent hormones such as androgen and thyroxin (T<sub>4</sub>) are needed for effective erythropoiesis. *In vitro* studies found that thyroxin stimulates erythropoiesis by both direct stimulation of red cell precursors and indirect through erythropoietin (EPO)-mediated effect. On the contrary excess T<sub>4</sub> suppresses thrombocytopoiesis (Sullivan & McDonald, 1992; Zitzmann & Nieschlag, 2004). Another important findings was the enhancement effect of androgen on EPO, this was found to be mediated through its nephrotrophic effect. However androgen played no role in the increased iron stores that was detected in patients with polycystic ovary syndrome (Barcelo et al., 1999; Escobar-Morreale et al., 2011).

On the other hand growth hormone (GH) replacement therapy was found to induce iron deficiency and increase hemoglobin concentration in children with short stature. Furthermore iron supplementation was recommended for any patient receiving GH treatment (Vihervuori et al., 1994). Similarly, cortisol showed a strong inhibitory effect on erythroid- progenitor cells (colony forming unit-erythroid (CFU-E)) on rat hematopoietic marrow. Meanwhile dexamethasone has a strong stimulatory effect on CFU-E of *in vitro* cultures of hepatic cells of mouse fetus (Singer et al., 1976; Golde et al., 1976).

The most logical association between hypopituitarism and anemia was in patients with sickle cell disease (SCD), patients with SCD could develop pituitary infarction. However this assumption was excluded in this case by the results of sickling test and hemoglobin electrophoresis (Prabhakar & Shalet, 2006; Rajasekaran et al., 2011).

In a trial to find out the effect of IDA on growth, anthropometric parameters of patients with IDA were

found to be lower than that of normal healthy controls (Bandhu et al., 2003; Soliman et al., 2009). This effect was explained by the inhibitory effect of hypoxia on insulin like growth factor-1 (Tsunawaki et al., 2013). These findings besides the above mentioned findings created a buzzle when facing a patient with IDA and hypopituitarism.

This case study of a teenager female patient presented with a triad of IDA, mild hepatosplenomegaly, and hypopituitarism. Her IDA was refractory to treatment with recombinant human erythropoietin injections, oral iron supplementation and vitamin C, anemia was further aggravated when patient received HRT in the form of prednisone, levothyroxine, and estrogen. These findings were contradictory to other research in which hormonal replacement therapy was found highly beneficial in correction of anemia in patients with Sheehan's syndrome (SS) (Gokalp et al., 2009). However the most common type of anemia in these patients was normocytic- normochromic anemia, while microcytic-hypochromic comprised only 45%. Interestingly hematological evaluation of patients with Sheehan's syndrome revealed conflicting results of reduced both serum iron and total iron binding capacity. Also, this case study was inconsistent to the findings of King et al. who reported correction of IDA in a 75- years male patient with hypopituitarism after initiation of hormonal replacement therapy (King et al., 2009). Nevertheless this patient received both testosterone and steroid replacement therapy, testosterone have a strong erythropoietic effects.

On the other hand the findings of this case report are albeit consistent with the findings of Nishioka and Haraoka who concluded that hormonal replacement with levothyroxine and hydrocortisone are insufficient to correct anemia in patients with hypopituitarism. They recommended the addition of GH and/or androgen to correct anemia (Nishioka & Haraoka, 2005). This case study showed that anemia is not only ineffectively managed with levothyroxin and hydrocortisone replacement therapy alone, but could be deteriorated further. Also, the findings of this study re-affirmed the findings of Christ et al. that GH treatment increases RBCs, Hb and PCV, meanwhile this case study showed increased MCV and serum ferritin which was contradictory to their study (Christ et al., 1997). These conflicting results could be explained that in this study patient was already on iron supplementation which was not the case in other studies, accordingly the possibility of iron deficiency as a consequence to GH enhancement of erythropoiesis did not exist.

The association between panhypopituitarism and hepatosplenomegaly (HSM) has been reported; furthermore HSM was improved after hormone replacement therapy, however the exact pathogenesis of HSM was unclear (Giacoia & MacGillvary, 1981). Interestingly these associations were more apparent in infants with panhypopituitarism, accordingly this could be explained by the hematopoietic activity of the liver and spleen in those infants (Herman et al., 1975).

On the other hand mild hepatosplenomegaly and IDA were found to be associated since nearly 50-years ago. Furthermore chronic IDA was found associated with growth retardation and hypogonadism in children (Halsted & Prasad, 1961; Rwegerera et al., 2015). In this case study HSM could be explained by the compensatory extramedullary hematopoiesis secondary to severe anemia, and reduction in size of the liver and spleen was expected after normalization of hematologic parameters.

## Conclusions

In conclusion this case report of a teenager female with IDA, mild HSM and hypopituitarism. Her anemia was aggravated with HRT and was improved with the addition of GH to her treatment. Based on these findings we recommended that the combination of IDA, HSM and hypopituitarism should be distinguished as a specific syndrome that should be mentioned in both hematology and endocrinology textbooks. Moreover, further research is needed to find out the exact association between panhypopituitarism, hepatosplenomegaly and IDA so as to suggest the proper management in these patients.

## Acknowledgments

The author wish to thank the secretary and paramedical staff at the hematology and BMT unit of Internal Medicine Department, AUH, Egypt for their help during follow up of the patient.

## Ethical consideration

A written informed consent was obtained from the patient prior to publication, however patient refused personal photographing even if without name.

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**How to cite this article:**

**Safaa A. A. Khaled (2015). Aggravation of Iron Deficiency Anemia after Hormone Replacement Therapy in a Patient with Hypopituitarism and Hepatosplenomegaly . Int. J. Adv. Res. Biol. Sci. 2(12): 324–329.**