CASE REPORT

Inherited haemochromatosis with C282Y mutation in a patient with alpha-thalassaemia: a treatment dilemma

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SUMMARY

A Caucasian 24-year-old female patient suffers from two hereditary disorders: alpha-thalassaemia, which is prevalent in Asia and rare in Europe, and haemochromatosis, which is prevalent among northern Europe and rare in Asia. The clinical presentation and management of one of these diseases is controversial for the other. She presented 5 years ago with a clinical picture of refractory iron-deficiency anaemia secondary to menorrhagia. On treating her with the standard iron therapy, her anaemia persists although with adequate iron stores. This prompted further investigations that revealed in addition to hereditary haemochromatosis, alpha-thalassaemia because of abnormal blood indices. The treatment of thalassaemia with either iron or blood transfusion is not advisable in haemochromatosis, while standard treatment of haemochromatosis with venesection will worsen the anaemia. As iron chelating agents were not approved in Australia for haemochromatosis, haematinics support was commenced with a satisfactory improvement of anaemia thus allowing for further venesection.

BACKGROUND

Alpha-thalassaemia is a very common haemoglobinopathy in southeast Asia that causes ineffective erythropoiesis.^{1–3} Hereditary haemochromatosis is a common disease that causes iron overload and is prevalent in Northern Europe.⁴ Nonetheless, the combination of both of them in one patient is extremely rare.¹

Alpha-thalassaemia is one of the most common haemoglobinopathies all over the world that leads to microcytic hypochromic anaemia with or without iron deficiency.^{1–3} About 95% of alpha-thalassaemia result from depletion of one or two of α -globin genes.⁵ The clinical picture of alpha-thalassaemia ranges from being symptom-free to a fatal condition with 4-gene deletion (Hb Bart's) known as hydrops fetalis.⁶ Approximately 10% of alpha-thalassaemia cases are distributed equally between Malaysia and Philippines.⁶ A third of the patients suffering from alpha-thalassaemia are located in Northern Thailand and Laos.⁷ Around one-third of Indian people suffer from alpha-thalassaemia.⁸ It has been argued that alpha-thalassaemia is associated with vitamin B₁₂ and folic acid deficiency due

to rapid red blood cells turnover, although full blood examination will not necessarily reflect these deficiencies due to associated low mean cell volume (MCV). Therefore, there is a strong recommendation to administer them in thalassaemia if clinically indicated.⁹

However, hereditary haemochromatosis is an autosomal recessive disease that occurs due to C282Y homozygosity of the Haemochromatosis (HFE) gene resulting in iron overload.^{4–10} Hereditary haemochromatosis affects about 5% of white northern European population and 90% of patients with haemochromatosis worldwide are from white European descent, mainly from Ireland with 13%.^{4–10}

What makes this stand out as an interesting case is the rarity of the combination of these two genetic disorders and its critical and challenging management. The presence and/or management of any of the two diseases will worsen the condition of the second one. On one hand, alpha-thalassaemia and/or its management by iron or blood transfusion can cause iron overload that worsens the existing hereditary haemochromatosis.^{4–10} On the other hand, venesection as an ideal treatment of haemochromatosis to remove the excess iron would worsen the anaemia.⁴ Therefore, a balance of treatment is crucial for successful management.

The importance of this case is to highlight the treatment dilemma that many clinicians may face worldwide. It also raises the need to study employing iron chelating agent in management of haemochromatosis to remove excess iron without deterioration of anaemia.

CASE PRESENTATION

A 19-year-old Caucasian female was referred to a general practitioner for investigation of increasing tiredness. She had been suffering from general weakness, fatigue and was frequently falling asleep in the study class, a few months prior to this referral. The patient suffered from menorrhagia since the age of 14 years and therefore was given contraceptive pills. As the heavy periods recurred recently, she had further investigations under the gynaecologist who recommended an intrauterine Mirena device. The rest of her medical history was unremarkable apart from an appendectomy and infrequent episodes of

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Figure 1 H&E stain of peripheral blood film showing microcytic hypochromic red blood cells. With features of thalassaemia and occasional target cells with 20× magnification.

viral and bacterial infection as well as being a vegetarian. Her full blood count (FBC) showed slight drop in haemoglobin (Hb) and significant low MCV. Iron studies showed low iron levels. Thus, iron supplement was given initially and improved her symptoms.

As the symptoms recurred with increasing fatigue and symptomatic anaemia with Hb of 70 g/L, the patient was treated with one unit of compatible blood and iron therapy in order to raise the Hb level to an acceptable level and improve the symptoms. The patient's symptoms improved during the course of the events.

Meanwhile, the patient was referred to the haematologist for further investigations.

The FBC at that point showed that the MCV was disproportionately lower than an iron deficiency picture and was not corrected despite iron therapy. Therefore, an Hb electrophoresis was requested to rule out a coexisting haemoglobinopathy. The Hb electrophoresis showed normal results that is not inline with beta-thalassaemia. A blood smear was requested, and the blood film showed microcytic hypochromic red cells in addition to occasional target cells (figures 1 and 2). As it was important to exclude a haemoglobinopathy, a DNA test was requested for

Figure 2 H&E stain of peripheral blood film with high magnification (60×).

alpha-thalassaemia. This showed two alpha gene deletions giving a diagnosis of alpha-thalassaemia trait.

It is worth noting that the reason of iron deficiency initially was due to severe menorrhagia.

She had regular appointments with her gynaecologist because of abnormal uterine bleeding, and she was diagnosed with endometriosis later on. After Mirena insertion, her menstrual period has improved significantly. Her Hb accordingly has improved to 100 g/L with amelioration of her symptoms.

A few months later, the patient had recurrence of her abnormal uterine bleeding and started to suffer increasing fatigue and sleepiness again. Further investigations with FBC, blood film, biochemistry and iron study were requested. The Hb was reduced to 80 g/L, and the MCV was low at 66 fL. All biochemistry results were normal. However, the unexpected result was the elevated iron stores (ferritin, 675 µg/L), which was a significant increase from the normal range (20–290 µg/L). As there was no explanation of the new higher level of iron accumulation, it triggered further investigations to enumerate a cause for this. Among the other tests, a blood sample was sent for HFE gene status analysis. This indicated that she is heterozygous for C282Y mutation.

The carrier status for haemochromatosis was not a surprise given that she was a Caucasian with an Anglo-Celtic ethnicity. This was the plausible cause for her elevated ferritin. Most of the cases of the alpha-thalassaemia are found around the north of India and some South Eastern Asian countries. The patient started an investigation of her roots and made up a family tree search. This revealed that her maternal great grandmother had an Asian (Indian) ethnicity. This would explain the inheritance of alpha-thalassaemia genes.

Treatment in a situation where a patient is anaemic and has iron overload has never been easier. Blood donation or venesection is recommended in iron overload associated with haemochromatosis. However, given her low Hb due to thalassaemia, this treatment should be monitored carefully. The patient was planned for venesection to avoid further ferritin increase; however, instead, a decision was made to optimise her Hb levels with the addition of vitamin B₁₂ and folic acid. It is difficult to balance between iron overload and to maintain the Hb level and also to minimise further accumulation of iron. Although iron chelators can potentially be used in such situations, there is currently no indication in Australia to use these agents for haemochromatosis.

The patient presented to hospital on one occasion with abnormal heavy bleeding, where she was given tranexamic acid and followed-up with her gynaecologist. The patient was commenced on a 6-month treatment of hormonal injection to try to control her endometriosis. A rise of Hb was achieved at 124 g/L (normal: 115–160), while the ferritin was 529 µg/L, which are considered as reasonable levels at that point. A volume-reduced venesection was commenced with improvement of her ferritin level to 300 µg/L mark.

Despite these events, she continues to live a normal life and practising nursing, although she has mentioned the fear of passing her hereditary disorders to any of her future offspring. She was offered genetic counselling.

The patient was fully aware at a young age of these interesting findings in her case. This had sparked her interest in the medical field and she later entered into the nursing profession to understand fully her condition. The patient is currently 24 years old and is practising nursing and has a normal life with the perspective to forming a family later on.

INVESTIGATIONS

FBC showed current Hb of 116 g/L (normal: 115–160). Normal white cell count and platelets.

Iron profile: serum iron of 15 µmol/L (normal: 10–33), iron binding capacity of 77 µmol/L (normal: 45–70), transferrin saturation 19% (normal: 16–50) and serum ferritin of 391 µg/L (normal: 20–290).

Blood film: microcytic hypochromic blood picture with occasional target cells and MCV of 76 fL (normal: 80–98) and MCHC of 25 pg (normal: 27–35).

Gene analysis/DNA mapping for alpha-thalassaemia showed two gene deletions and heterozygous C282Y missense mutation at *HFE* gene.

Hb electrophoresis showed normal results.

The liver and kidney function as well as heart function were within normal limits.

Serum ceruloplasmin was slightly high at 480 mg/L (normal: 150–450).

DIFFERENTIAL DIAGNOSIS

Reaching the final diagnosis was challenging. The patient was initially diagnosed with alpha-thalassaemia due to abnormal blood indices in association with IDA. Although the patient has fair complexion and appears of Caucasian decent, a careful history revealed a distant grandmother who originated from India. Fluctuating Hb as well as iron deficiency that converted to iron overload was not explained by this diagnosis. Of note, there was a rapid improvement of Hb and iron stores with the improvement of her menorrhagia. These contradictory presentations and investigations prompted the haematologist to track her ethnicity of her roots. This showed her father is Caucasian with an Angelo-Celtic ethnicity with great-grandmother coming from India. The new information guided the clinician to investigate her for both thalassaemia and haemochromatosis, which were both positive.

Numbers of differential diagnoses include:

1. anaemia of chronic illness
2. increased iron intake
3. haemochromatosis
4. alpha-thalassaemia and beta-thalassaemia
5. haemoglobinopathies.

TREATMENT

Treatment for this patient was a challenge. Ideally, treatment of haemochromatosis would be by venesection, which was not possible to start with in this case due to severe anaemia. Iron-chelating agents are not approved in Australia for this indication, although it seems to be not unreasonable solution in this case. Treatment of anaemia associated with alpha-thalassaemia is consistent with blood transfusion and/or iron therapy if the patient is showing low iron stores as it happened initially in this case. However, the risk of iron overload exists due to haemochromatosis. The decision was made strategically to treat the patient on two stages: first, to improve the anaemia using vitamin B₁₂ and folic acid to improve the Hb without increasing the iron stores. At the same time, the patient was treated by the gynaecologist to improve her uncontrolled menorrhagia. The second stage was to commence volume-reduced venesection to remove the excess iron. The plan was successful, and the patient has improved significantly in both well-being and in the laboratory markers for both anaemia and iron stores. Genetic counselling is worthwhile in patients with childbearing potential, specially with such hereditary disorders.

OUTCOME AND FOLLOW-UP

Patient condition improved with continuous monitoring and careful management by the haematologist and gynaecologist. Social and psychological impacts were considered, especially her fear of passing her rare conditions to future generation.

Regular follow-up with iron studies and FBC was instated.

DISCUSSION

Usually patients with alpha-thalassaemia trait do not need treatment. However, in rare cases, there may be a significant drop of Hb level due to aplastic crisis or similar conditions.^{1–3 5–8} When a major drop of Hb occurs, the patient needs blood transfusion.^{1–3 5–8} The blood transfusion may result in worsening the iron overload.^{11 12}

The current practice of treatment of haemochromatosis depends on removal of excess iron via venesection.^{12 13} Chelating agent is an alternative but not yet approved in Australia for this particular indication.¹¹ There are exploratory trials to establish hepcidin supplement as a treatment of hepcidin deficiency associated with ineffective erythropoiesis.^{12 14 15}

Our unique case suffers from haemochromatosis and thalassaemia in conjunction with anaemia. Excess iron may result

Patient's perspective

- For several years I had suffered from continuous fatigue and weakness, which at the time, my general practitioner believed was caused from several other factors, including being a vegetarian. But after no improvement with oral iron supplements, struggling through my studies and being constantly exhausted for most of my teenage years, I finally sought out a specialist review with further investigations and referrals that were required to find the cause. Being diagnosed and treated initially for the alpha-thalassaemia with the transfusions to increase my blood count level made a large impact on my life, I was able to undertake more activities and enjoy life.
- Through the treatment that I received, I found an interest in medicine and helping people. I completed my studies in Bachelor of Nursing, but towards the end of my degree my fatigue increased and I began falling asleep frequently, including whilst I was driving. After further investigations with my general practitioner I was sent back to the haematologist for the management of both illnesses. Now with the combined effort with my gynaecologist and haematologist, some lifestyle changes including reducing shift work hours, exercising regularly and diet-control, my symptoms are mostly controlled and I live a relatively normal life.

Learning points

- Consider using iron-chelating agents in exceptional cases like combined thalassaemia and haemochromatosis.
- The use of vitamin B₁₂ and folic acid in management of these cases when high potential of iron overload is worthwhile.
- Consider to exclude causes of iron overload in persistent high ferritin even in cases known to have iron-deficiency anaemia.
- Physician should consider mixed ethnicity when evaluating their patients especially in multicultural communities like in Australia and other places in the world.

in internal organ damage, especially the liver, pancreas and heart.^{4 12 13} The clinical decision was to give folic acid and vitamin B₁₂ to promote Hb formation without causing iron excess. Otherwise, the patient would receive blood transfusion or iron with all its possible complications and hazards to improve Hb along with chelating agent to prevent iron overload.^{9 12} A study conducted by Oliveira and colleagues¹ had evaluated the presence of C282Y (hereditary haemochromatosis) among 102 patients with alpha-thalassaemia. Only one patient had demonstrated C282Y gene with percentage of 0.98%.

In conclusion, our case highlights the importance of taking into consideration different factors that may influence iron metabolism. Balancing iron demand and overload together with other haematinics supportive treatment is crucial for successful management in such complex cases.

Contributors MAA interviewed the patient, gathered the information and drafted the manuscript. FH collected the data and drafted the manuscript in its final form. USV gathered the results and photography and contributed in the management and in writing the manuscript. AAK treated the patient and was responsible for all aspects of manuscript writing and reviewed it in its final form.

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