INTRODUCTION

Anaemia is a common condition seen in clinical practice. WHO defines anaemia as a haemoglobin (Hb) level below 13.0g/dL in men and below 12.0g/dL in women [1]. In the elderly population, iron deficiency, gastrointestinal blood loss, chronic diseases, vitamin B12 and folate deficiency, and myelodysplastic disease are among the many causes of anaemia. Anaemia can also be the first sign of hypothyroidism even though it is more common in those with overt hyperthyroidism [2]. This case emphasizes the importance of including thyroid function test as part of the work up for anaemia, particularly in elderly patients with refractory anaemia. Identifying and treating this patient’s hypothyroidism improved his Hb significantly.

CASE PRESENTATION

A 68-year-old gentleman was referred to our primary care clinic for investigation and management of refractory anaemia. He had underlying ischaemic heart disease with severe mitral regurgitation and had undergone coronary artery bypass grafting (CABG) six months earlier. He also had underlying type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) stage 3b. He was on aspirin, clopidogrel, s/c actrapid, atorvastatin, frusemide, bisoprolol, omeprazole and bisacodyl. Following CABG, he had two admissions. The first admission was a month after CABG and the reason for admission was for symptomatic anaemia during which he presented with chest pain. On admission, his haemoglobin (Hb) was 7.6g/dL, with normal mean cell volume (MCV) at 99.8fL and normal mean cell haemoglobin (MCH) at 31.3pg. The white cell and platelet count were normal at 8.97 x 10³/µL and 191 x 10³/µL respectively.

He was transfused immediately with two units of packed red blood cells due to the fear that his low Hb would exacerbate his ischaemic heart disease. The
initial differential diagnosis was anaemia of chronic disease due to the underlying CKD.

Inpatient investigations showed a positive faecal occult blood test (FOBT) with low serum iron (7.4µmol/L) but a high ferritin level (673µg/L). The serum transferrin was normal at 3.0 g/L and the total iron binding capacity (TIBC) was also normal at 75.3 µmol/L. However, his Unsaturated Iron Binding Capacity (UIBC) was raised at 46.7 µmol/L by 10% which may suggest a coexisting iron deficiency anaemia and anaemia of chronic disease. Both serum vitamin B12 and folate levels were within normal ranges. A peripheral blood film (PBF) showed normochromic normocytic RBCs with presence of macrocytes. The diagnosis made by the physician at this point was anaemia of chronic disease with underlying infection or inflammation. As his symptom improved, he was discharged with iron tablets and planned for outpatient oesophago-duodenoscopy (OGDS) and colonoscopy to look for any source of gastrointestinal bleeding.

Three months later, he presented with oliguria and was clinically dehydrated. He was admitted for acute renal impairment secondary to dehydration when his serum creatinine was elevated at 444µmol/L. His estimated glomerular filtration rate (eGFR) was 12 mL/min/1.73m2. His Hb level remained low at 9.3g/dL despite iron supplementation. Repeat blood film then showed hyperchromic and macrocytic RBCs with a MCV of 104.7 fL, MCH of 33.6 pg. He was given intravenous rehydration which improved his condition. He was then discharged home with all his regular medications including iron tablets. He was given a referral to our primary care clinic to look into his anaemia. Figure 1 depicts the timeline of his illness.

During the first consultation at the primary care clinic, he complained of constipation and feeling of lethargy for the past year. He denied shortness of breath, palpitation or chest pain. He has no family history of thyroid disorders or blood dyscrasias, however, his elder sister had colorectal carcinoma. He did not smoke or drink alcohol. On examination, he looked pale with an apathetic facial expression and thinning of the eyebrows. He was not icteric nor oedematous. His blood pressure was 100/60 mmHg, and pulse rate was 68 beats per minute. He was slow to respond to questions and had slow movements. His skin and hair were dry and his nails were brittle. There was no xanthelasma, tendon xanthoma or goitre seen. There was no thyroid nodule on palpation. Cardiovascular examination revealed a grade four pan-systolic murmur loudest at the apex. Lung examination was unremarkable. Abdominal examination was normal and per rectum examination revealed no mass or malaena. His ankle reflexes were delayed.

His latest blood test results showed a low Hb of 7.4g/dL (macrocytic) with a high MCV of 107.4 fL, high MCH of 35.6 pg with normal total white blood cells, 4.51 x 10^3/µL and platelets, 181 x 10^3/µL. His urea was raised at 12 mmol/L, and his creatinine was 190 µmol/L. A repeat blood film showed a macrocytic picture. Serum vitamin B12 and serum folate were normal. His liver function test was normal. Thyroid function test (TFT) was ordered. Urgent OGDS and colonoscopy were arranged as he was unsure about his previous appointment date for these investigations. Further progress of FBC and TFT is shown in Table 1 below.

At the subsequent follow up, the patient’s condition remained the same. His T4 level was low at 2.7 pmol/L (11.5 – 22.7) and TSH was markedly raised at 58.4 mIU/L (0.550 – 4.780). His anti-thyroid Peroxidase (anti-TPO) was also elevated at 783 IU/mL (<35.0 IU/mL). Meanwhile, his OGDS revealed antral and pyloric inflammation, with a healing ulcer near the pylorus. His rapid urease test was negative. On colonoscopy, there were three colonic polyps seen at the transverse colon. Histopathological examination reported the duodenal biopsy was suggestive of peptic duodenitis with reactive Brunner’s gland hyperplasia while the hepatic flexure polyp found a tubular adenoma suggestive of low-grade dysplasia.

He was informed of the Hashimoto’s disease diagnosis. He understood that he would require lifelong treatment with thyroxine. Thyroxine was started at 50mcg OD and slowly tapered up to 100mcg OD. This improved his Hb level significantly. He was also arranged for three-yearly colonoscopies and was prescribed with Omeprazole 20mg BD for at least two months.
Table 1 Significant blood test results for this patient

<table>
<thead>
<tr>
<th>Week</th>
<th>Hb (g/dL) (13.0-17.0)</th>
<th>MCV (fL) (80-100)</th>
<th>MCH (pg) (27.0-34.0)</th>
<th>FT4 (pmol/L) (11.5-22.7)</th>
<th>TSH (mIU/L) (0.55-4.78)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st visit</td>
<td>7.4 (high)</td>
<td>107.4 (high)</td>
<td>35.6 (high)</td>
<td>2.7</td>
<td>58.40</td>
<td>L-Thyroxine started at 50mcg OD</td>
</tr>
<tr>
<td>Week 3</td>
<td>9.0 (high)</td>
<td>104.4 (high)</td>
<td>33.3 (high)</td>
<td></td>
<td></td>
<td>L-thyroxine 50mcg OD</td>
</tr>
<tr>
<td>Week 9</td>
<td>8.8 (normal)</td>
<td>99.9 (normal)</td>
<td>31.1 (normal)</td>
<td>14.3</td>
<td>18.96</td>
<td>L-thyroxine 75mcg OD</td>
</tr>
<tr>
<td>Week 13</td>
<td>11.0 (normal)</td>
<td>94.8 (normal)</td>
<td>29.3 (normal)</td>
<td>20.3</td>
<td>9.35</td>
<td>L-thyroxine 100mcg OD</td>
</tr>
<tr>
<td>Week 20</td>
<td>12.6 (normal)</td>
<td>89.4 (normal)</td>
<td>27.9 (normal)</td>
<td></td>
<td></td>
<td>L-thyroxine 100mcg OD</td>
</tr>
<tr>
<td>Week 30</td>
<td></td>
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</table>

Figure 1: Timeline of presenting illness

DISCUSSION

This case highlighted the importance of differentiating between the aetiologies of anaemia as the prognosis and treatment are different. It is important to identify and treat anaemia as it is associated with increased risk of hospitalization and mortality in the elderly [3]. In Malaysia, the overall prevalence of anaemia among the elderly is 35.3%. The highest prevalence of anaemia was found among Indians, those with increasing age, those with history of hospital admission, and those with diabetes mellitus [4].

It was a challenge to establish the exact cause of anaemia in this patient because of his multiple comorbidities. The patient was at risk of developing iron deficiency anaemia due to gastrointestinal bleeding as he was on aspirin, which was reflected by the positive FOBT, low iron and raised UIBC at the first admission and a healing ulcer on OGDS. With a diagnosis of CKD, he was also at risk of developing anaemia of chronic disease. Hence, hypothyroidism was not initially considered.

The prevalence of anaemia among hypothyroid patients is higher than the general population (i.e. 75% vs. 32%) [5]. It was also observed that the higher the TSH level, the higher the prevalence of moderate to severe anaemia [6]. One of the causes of hypothyroidism is Hashimoto’s thyroiditis. It is an autoimmune disorder in which antibodies directed to the thyroid gland lead to chronic inflammation [7]. The resulting inflammation often leads to an underactive thyroid gland. It is said that it takes about ten years to be diagnosed with Hashimoto’s disease between the start of the autoimmune attack and when the person is eventually diagnosed [7]. Hashimoto’s disease is common in females, and younger age groups between the age of 30 and 50 years [8,9].

In patients with thyroid disease, although abnormalities in the haematological parameters have been noted, the exact mechanism of the thyroid hormones actions on human erythropoiesis is not clearly understood. A decreased thyroid hormone is known to adversely affect erythropoiesis, and this alters the RBC morphology. The RBCs in hypothyroid patients may present with a normochromic normocytic (65.9%), microcytic hypochromic (22.72%) or macrocytic (11.36%) picture [6]. It was also found that about 68.9% of anaemic hypothyroid patients had a positive anti-TPO level [6]. In addition, there is a significant positive relationship between the concentrations of free thyroid hormone and haemoglobin, haematocrit, and erythrocyte count, with a simultaneous negative correlation between TSH levels and the serum iron concentration and transferrin saturation [10].

Experimental studies demonstrated an enhanced erythroid colony growth induced by free triiodothyronine, thus, in hypothyroid patients, the number and proliferative activity of erythroid cells in the marrow is reduced [11]. Hypothyroid patients also show a decreased plasma concentration of erythropoietin. All the observed changes are regarded as physiological adaptations to the reduced oxygen requirement of the tissues, due to the diminished basal metabolic rate in hypothyroidism [11]. Successful
treatment of hypothyroid patients with Hashimoto’s thyroiditis and restoration of the euthyroid state is associated with a decrease in hepcidin concentration that follows the observed dynamics of iron homeostasis. This leads to improvement in erythropoiesis [12].

In conclusion, anaemia may be one of the first signs of hypothyroidism. Hence, hypothyroidism should always be considered in patients with anaemia, especially in those with uncertain aetiology.

Conflict of Interest
Authors declare none. Verbal informed consent for patient information was obtained from the patient himself.

Acknowledgement
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Author’s Contribution
SAWA prepared the first draft of the case report. SAR and MSMY contributed to the critical revision of the case report. All authors read and approved the final version.

REFERENCES