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Case Report Open Access

Challenges in Diagnosing Pernicious Anemia: A Case Series

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Introduction

Pernicious anemia is thought to be rare in Africa, with the biggest burden of anemia cases attributed to the neglected tropical diseases (NTDs), Malaria and HIV [1]. However some reports have reported pernicious anemia to be the commonest cause of megaloblastic hemopoiesis in an African context [2]. In the same study, isolated folate deficiency was noted to be rare. Pernicious anemia needs prompt diagnosis to avoid long-term sequelae of the condition [3]. However this is not the case, more so in resource limited settings due to a multiplicity of factors which include low index of suspicion, concurrence with microcytic anemia and high costs of workup. The two reported cases demonstrate this and hopefully will enhance our diagnostic capability of this rather debilitating condition if treatment is delayed.

Case 1

A 42 year old woman presented to our institution with history of recurrent dizziness, dyspnoea and headaches, with several episodes of laboratory confirmed anemia over the preceding four years. She had been seen in several hospitals, transfused fresh blood on three occasions, and sent home on iron and folate supplements every time. She also reported numbness affecting her legs and feet bilaterally over the preceding year. One week before presentation, she had developed progressive pain and swelling on the right ankle. She reported longstanding heartburn and dyspeptic symptoms, on long-term, intermittent treatment with proton pump inhibitors. On examination, she was in fair general condition, her BP was 135/85 mmHg, respiratory rate of 21 breaths per minute and pulse rate of 96/min. She was saturating at 96% on ambient air. She had conjunctival pallor. She had mild, tender pitting edema on the right ankle and tender calf on the same leg. Other systemic exam was normal. A full hemogram, peripheral blood film, *Helicobacter pylori* (*H. pylori*) fecal antigen test, urea, creatinine, electrolytes and a Doppler ultrasound were ordered as initial investigations and the results are shown in Table 1.

Investigation		Findings	Reference ranges
Full Hemogram	Erythrocyte count (mm^3)	1,500,000	4,500,000-5,900,000
	Mean corpuscular volume (fl)	110.3	76-96 fl
	Hematocrit (%)	16.5	41.0-53.0
	Hemoglobin (g/dl)	6.5	12-16(women)
	Mean corpuscular haemoglobin (pg)	43.6	26-32
	Mean corpuscular hemoglobin concentration (g/dl)	39.5	33-36
	Red cell distribution width (%)	28.6	11.5-14.5
	White cell count (per mm^3)	6600	4500-11000
	Platelet count (per mm^3)	194,000	140,000-400,000
Urea (mmol/l)		5.8	1.7-8.3
Creatinine (µmol/l)		56	44-80
Potassium (mmol/l)		4.2	3.5-5.5
Sodium (mmol/l)		142	135-145
Helicobacter pylori fecal antigen		Negative	

Table 1: Laboratory findings for case 1 with corresponding reference ranges where applicable.

The Doppler ultrasound showed deep venous thrombosis on the right calf and the patient was admitted for parenteral heparin therapy. A diagnostic OGD was performed as inpatient in view of her longstanding reflux and dyspeptic symptoms and the hemogram indices. Some of the images obtained, together with the findings on the peripheral blood film are shown in Figures 1 and 2. The samples obtained endoscopically confirmed chronic atrophic gastritis affecting the gastric body and antrum.

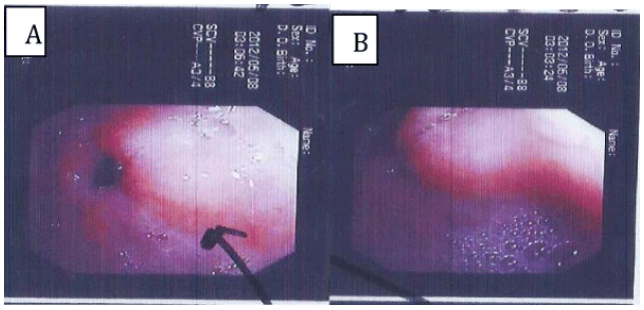

Figure 1: OGD images showing antral (A) and body (B) gastritis.

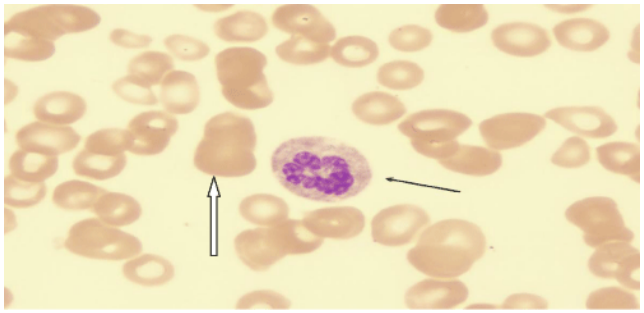

Figure 2: Peripheral blood film showing macro-ovalocytes (thick arrow) and a hypersegmented neutrophil (thin arrow).

Methylmalonic acid levels in urine were requested; the results were 271 mg/g/creat [4-15]. With the information gathered so far from the clinical aspects and the focused investigations, a diagnosis of megaloblastic anemia due to pernicious anemia was made and therapy instituted with daily hydroxocobalamin injections (1000 µg) for 1 week, weekly injections for one month, and monthly injections thereafter. Table 3 shows the hemogram features after one year of treatment

The numbness in the legs resolved after three months of initiation of therapy, and discontinuation of warfarin prophylaxis was done after 6 months with no recurrence of DVT.

Case 2

The second patient was a 36 year old female, also with several previous admissions in various hospitals with epigastric pains and anemia, though not in our facility. She had history of blood transfusion three months before her presentation. She also reported very troublesome involuntary movement of her feet bilaterally at the ankle joint, initially episodic but later worsening and becoming more frequent. These movements occurred when at rest and not weight bearing on her feet. She also reported severe pain on the posterior aspect of the lower limbs bilaterally. On examination, her vital signs were within normal ranges, had conjuctival pallor and a yellowish, lemon-like facial tinge as shown in Figure 5A. Other than brisk patellar reflexes and a tender epigastrium, the remainder part of the examination was unremarkable. The urea, creatinine and electrolytes were normal; fecal occult blood, *H. pylori* fecal antigen were all negative. The platelets and white cells in the hemogram were also normal. The abnormal red cell indices in the hemogram are shown in Table 2 while Figure 3 shows the endoscopic images of the gastric fundus and antrum. Like in the first patient, the histology of the gastric specimens showed severe atrophic gastritis, as shown in Figure 4 and *H. pylori* was positive. Her methylmalonic acid urinary levels were elevated at 356 mg/g/creat. The treatment included *H. pylori* eradication therapy (amoxicillin, clarithromycin, omeprazole) for 14 days, and intramuscular hydroxocobalamin. The neurologic symptoms resolved after two months of therapy.

Red cell index	Results
Erythrocyte count	1,460,000/mm^3
Hemoglobin	6.4 g/dl
Hematocrit	19.8%
Mean corpuscular hemoglobin	44.1 pg
Mean corpuscular volume	115.4 fl
Red cell distribution width	29.6%

Table 2: Red cell indices of case 2.

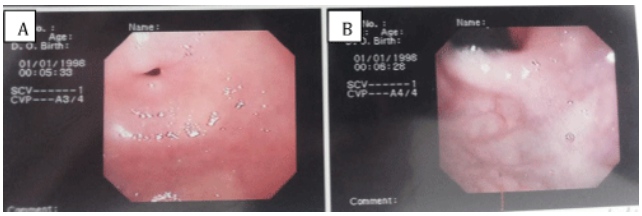

Figure 3: OGD images from the second case showing antral (A) and body (B) gastritis.

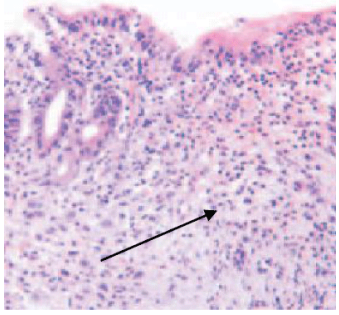

Figure 4: Histological preparation from the second patient showing absence of glands (arrow), Hematoxylin and Eosin (H & E), ×76.

Treatment Results

Table 3 shows the remarkable improvement in the red cell indices after 6 months treatment for the first patient and 3 months for the second patient. Figure 5 show changes in the facial appearance of the second patient after treatment.

Red cell index	Results			
	Case 1		Case 2	
	Before treatment	After one year of treatment	Before treatment	After 3 months of treatment
Erythrocyte count (per mm^3)	1,500,000	5,030,000	1,460,000	4,020,000
Hemoglobin (g/dl)	6.5	15.6	6.4	10.9
Hematocrit (%)	16.5	44.9	17.8	32.7
Mean corpuscular volume (fl)	110.3	89.2	115.4	81.2
Mean corpuscular haemoglobin (pg)	43.6	31.0	44.1	27.1
Red cell distribution width (%)	28.6	14.1	27.8	19.1

Table 3: Red cell indices for the two patients before and after treatment.

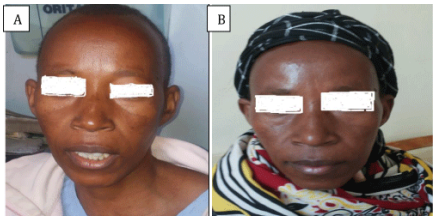

Figure 5: Facial appearance of the second patient; before treatment (A) and after 3 months of I.M hydroxocobalamin (B).

The two patients are currently continuing with their maintenance monthly injections of hydroxocobalamin and remain healthy.

Discussion

The recognition and treatment of vitamin B_{12} deficiency is critical since it is a reversible cause of bone marrow failure and demyelinating nervous system disease [4]. The two causes of severe vitamin B_{12} malasbsorption is partial gastrectomy and pernicious anemia, with the latter being the predominant cause [5]. Pernicious anemia (PA) is a macrocytic anemia that is caused by vitamin B_{12} deficiency, as a result of intrinsic factor deficiency. PA is associated with atrophic body gastritis, whose diagnosis is based on histological confirmation of gastric body atrophy [6]. Though the term PA is sometimes synonymously with cobalamin deficiency, to avoid ambiguity the term is commonly preserved for conditions that result from impaired secretion of intrinsic factor and atrophy of the oxyntic mucosa [7]. It is also recognized that most of these patients present mainly with neurologic symptoms [8,9]. Recent evidence point towards the role of *H. pylori* in atrophic gastritis though there is still no consensus whether to include PA among the long-term consequences of *H. pylori* gastritis. After clinical impression of the condition is made, the first step in the diagnostic workup is to check the hemogram and peripheral blood film for features of macrocytosis. If macrocytic anemia is confirmed, then checking for methylmalonic acid levels in serum or urine will confirm vitamin B_{12} deficiency [5]. Homocysteine levels in serum can also be used but is less specific [10,11]. The next step is to find out the cause of the deficiency; if the patient consumes sufficient amounts of vitamin B_{12}, then malabsorption is the answer. Without history of gastrectomy, then anti-intrinsic factor antibodies or anti-parietal cell antibodies will be indicative of PA [5]. However, some experts recommend endoscopy to confirm gastritis and rule out gastric cancers, which have been noted to be increased in PA [12].

The treatment of vitamin B12 deficiency due to malabasorption/PA is parenteral hydroxocobalamin and is life long, with recurrence of symptoms on discontinuation [13,14]. Our patients both presented with longstanding symptoms of both anemia and neurological symptoms. Though full blood counts were done severally in other hospitals, they continued getting the wrong treatments in form of blood transfusions, iron and folate supplementation instead of being subjected to further diagnostic workup. Methylmalonic acid levels can be analyzed either in serum or in urine [4,15]; the latter was chosen due to availability. Occurrence of deep venous thrombosis in vitamin B_{12} deficiency, like it occurred in the first patient has also been recognized elsewhere [16]. The two cases highlight the importance of this condition, and the importance of including vitamin B12 deficiency as a possible differential diagnosis in patients presenting with symptoms of anemia or unexplained neurological symptoms.

Summary

Two patients presented to our hospital, which is a regional referral hospital, with similar symptoms of anemia, neurological symptoms, and longstanding dyspepsia. Both patients had been transfused severally in other hospitals and discharged home on iron and folic acid supplements, but with no notable change in their red cell indices or their symptom profile. After thorough clinical evaluation, hemogram features, methylmalonic acid levels determination in urine and oesophagogastroduodenoscopy (OGD) with histological examination of multiple gastric specimens, a diagnosis of pernicious anemia was made in the two patients. Therapy was instituted with parenteral

hydroxocobalamin and a remarkable improvement in the red cell indices and clinical profile was observed.

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