Copper Deficiency with 20q Deletion and a Paroxysmal Nocturnal Haemoglobinuria Clone Presenting with Bicytopenia

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Abstract Copper plays an essential role in numerous enzymatic reactions in the human body and hypocupremia manifests itself as cytopenias and/or neuropathy. Copper deficiency is also a mimic of dysplasia, and this may cause diagnostic difficulties with true myelodysplasia. In this case report, we present a patient with anaemia, thrombocytopenia and marginally decreased leucocyte count, who was found to have low copper levels. In addition, he had isolated 20q deletion and a small paroxysmal nocturnal haemoglobinuria clone, which have not been reported previously. His counts normalized after steroid therapy followed by copper supplementation. This case is presented to highlight the fact that copper deficiency may be present without the characteristic morphologic changes, and may be coexisting with other abnormalities.

Keywords Copper deficiency · 20q deletion · Isolated 20qdel · PNH · Paroxysmal nocturnal haemoglobinuria

Introduction

Copper is a trace mineral that plays an essential role in multiple enzymatic processes in the human body [1, 2]. Copper-incorporated ceruloplasmin, a ferroxidase, converts Fe^{2+} to Fe^{3+} , which then binds to transferrin and is transported [3]. Copper-dependent cytochrome-c oxidase is

required for incorporation of iron into the heme molecule [1, 2]. Copper deficiency also results in decreased activity of superoxide dismutase in the erythrocyte membranes, leading to shortened RBC survival [4]. Hephaestin, also a copper-dependent ferroxidase and a ceruloplasmin analogue, is involved in the basolateral transport of iron into the circulation after intestinal absorption into enterocytes [5]. Copper deficiency impacts hematopoietic cells directly as well as indirectly through its interface with iron transport and metabolism. The reported manifestations of such deficiency have been described as cytopenias, predominantly anemia and neutropenia; and/or neurological complaints [6, 7]. In addition, it is also a mimic of myelodysplasia [6].

We present a curious case of a 42 year old man with anaemia, thrombocytopenia and marginally decreased white blood count (WBC), who was subsequently found to have low copper levels. In addition, he had isolated 20q deletion and a small paroxysmal nocturnal haemoglobinuria (PNH) clone, which have not been reported previously.

Case report

The patient presented from an outside institution with a history of anaemia for approximately 6 months and a single transfusion for low haemoglobin (7.5 g/dL). He denied intake of any supplements or alternative medicine remedies. On examination, there was pallor, but no lymphadenopathy or organomegaly. The complete blood count (CBC) showed: WBC, $4.33 \times 10^9/\text{L}$ (normal range $4.4\text{--}11 \times 10^9/\text{L}$) with a differential count of 29 % neutrophils, 64 % lymphocytes, 6 % monocytes and 1 % eosinophils; RBC, $2.8 \times 10^{12}/\text{L}$ (normal range $4.5\text{--}6.5 \times 10^{12}/\text{L}$); Hb, 9.7 g/dL (normal range 14–18 g/dL); HCT, 28.6 % (normal range 42–54 %); MCV, 101.4 fL (normal range 80–96 fL); MCH,

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Fig. 1 **a** Photomicrograph of 1st bone marrow aspirate showing erythroid hyperplasia and mild dyserythropoiesis (Leishman stain, Oil immersion lens). **b** Photomicrograph of 2nd bone marrow aspirate showing dyserythropoiesis with internuclear bridging (Leishman stain, Oil immersion lens)

34.4 pg (normal range 27–31 pg); MCHC, 33.9 g/dL (normal range 32–37 g/dL); RDW, 19.4 % (normal range 11.6–14 %); and platelets, $39 \times 10^9/L$ (normal range $150\text{--}400 \times 10^9/L$). A peripheral smear examination showed a macrocytic anaemia. Bone marrow aspirates performed on two occasions revealed erythroid hyperplasia and dyserythropoiesis (Fig. 1a, b). The trephine biopsy revealed hypercellular marrow with erythroid hyperplasia. Serum Vitamin B12 level was normal. Serum lactate dehydrogenase was within reference ranges. A direct antiglobulin test with polyspecific sera against IgG/C3d was negative. Stool examination as well as an oesophagogastrroduodenoscopy was unremarkable. An abdominal ultrasound examination was normal. Cytogenetic examination showed a normal karyotype of 46, XY. FISH testing for myelodysplastic syndrome (MDS)-specific anomalies revealed del20q in 32 % of

cells. Testing for PNH using flow cytometry showed a small clone (1.2 %) of WBCs with the PNH phenotype.

The patient was started on Prednisolone (Wysolone®, Wyeth Limited) with a dose of 60 mg/day for 5 days followed by tapering over 4 weeks. Subsequent CBCs showed an apparent response to steroids with the haemoglobin rising to 11.1 g/dL and platelets rising to $104 \times 10^9/L$ after 4 months (Fig. 2). However, given the lack of complete response and persistent macrocytosis, the possibility of copper deficiency was considered. Serum copper level testing revealed copper levels to be 6.705 $\mu\text{mol/L}$ (reference range 11.018–22.036 $\mu\text{mol/L}$, bathocuproine colorimetric method). Serum ceruloplasmin level was normal. Copper supplementation with 10 mg copper sulphate (Bevon®, Zuventus Healthcare Limited, two capsules twice a day) was started and steroids were tapered off. The CBC completely normalized over the next 16 months (Fig. 2). The most recent haemoglobin was 14.1 g/dL, and the serum copper level was also normal at the time of haematological remission (12.277 $\mu\text{mol/L}$, Fig. 2). A repeat bone marrow was not performed as the patient's haematological parameters recovered. The patient was eventually lost to follow up after the last CBC.

Discussion

The causes of copper deficiency are varied and may be due to inadequate intake or excessive loss. Inadequate intake of copper may arise due to prolonged total parenteral nutrition coupled with inadequate supplementation and unsupplemented milk used as a sole nutrition source for low-birth weight infants [8]. Acquired copper deficiency as a consequence of malabsorption may be seen in celiac disease, cystic fibrosis, prolonged diarrhea; post-gastrectomy and jejuno-ileal bypass surgery [8]. Increased zinc intake via zinc supplements as part of therapy or inadvertently through denture adhesives is a well documented cause of acquired copper deficiency [9]. Excessive loss of ceruloplasmin-bound copper in nephrotic syndrome may also cause hypocupremia [8].

With respect to the current case, the aspirates did not have the characteristic morphologic clues to an underlying copper deficiency [6]. The lack of morphologic clues to the diagnosis may be due to copper levels not being low enough to be reflected via morphologic changes. Also, he did not have any overt reason for low copper levels. There were no signs or symptoms of a malabsorption syndrome. Hence, a low threshold for triggering tests for nutritional deficiency might be indicated, especially in a young patient with refractory cytopenias and dyspoiesis. In addition, this is the first patient with copper supplementation-responsive cytopenias who has a concurrent FISH abnormality and a

Fig. 2 Timeline of select CBC parameters prior to and post-therapy with steroids and copper supplements

small PNH clone [7, 10–12], raising the question: is our patient then an MDS with associated copper deficiency or essentially copper-deficiency mimicking dysplasia?

20q deletion as a single anomaly are not presumptive evidence of myelodysplasia and have been found in a number of hematologic and non-hematologic conditions [13]. When present, isolated del20q are predominantly associated with erythroid and megakaryocytic abnormalities [14]. It has been suggested that a subset of refractory immune thrombocytopenia with isolated del20q might represent a form of indolent MDS [15]. In a series of 62 patients, those with isolated del20q had lower platelet counts, lower marrow blast counts, and higher reticulocyte counts, when compared to those without isolated del20q [16].

Small PNH clones have been demonstrated in MDS and were typically seen in those presenting with marrow failure, and were less likely to undergo leukemic transformation. Refractory anemia was the most common type of MDS associated with a PNH clone, and characteristically had less severe morphologic abnormality of blood cells, higher degree of thrombocytopenia, were more likely to have normal karyotype, had less risk of transformation and higher rate of response to cyclosporine [17, 18]. A single study of 32 MDS patients postulated that copper deficiency may be a consequence of iron overload, rather than an inducer of dysplasia [19].

At 20 months, this patient's blood counts have responded to steroids and copper supplementation. The fact that steroids alone did not suffice, and copper replacement was necessary to normalize the CBC, makes copper deficiency a likely cause of the cytopenias. The haematological response

noted with copper supplementation, even with the presence of single lineage dysplasia, makes it difficult to label this as a myelodysplasia at the present time. However, the presence of clonal abnormalities makes it imperative that his blood counts are monitored carefully in the future.

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