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CASE REPORT

Unexplained chronic leukopenia treated with oral iron supplements

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Abstract *Case* A 67-year-old woman known to have iron deficiency anemia and persistent unexplained chronic leukopenia was cared for by our medical center for about 16 years. During this period she was examined thoroughly and diagnosed to have chronic idiopathic neutropenia (also known as chronic benign neutropenia). Her iron deficiency was attributed to nutritional factors and she was non-compliant with her oral iron supplements. The patient fully received her iron supplement medication by nursing staff for two and a half months during an unexpected prolonged hospital stay after her suffering an acute ischemic cerebrovascular accident. An astonishing outcome was that in addition to having her iron deficiency anemia treated, her long-term unexplained neutropenia was also corrected. *Conclusion* Some patients diagnosed with chronic idiopathic neutropenia and clinically present as having unexplained chronic neutropenia might actually be suffering from a form of not yet described iron deficiency induced neutropenia.

Keywords Anemia · Iron deficiency · Leukopenia · Neutropenia · Patient adherence

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Impacts on practice

- Clinicians should consider the possibility that idiopatic chronic leukopenia may be caused by iron deficiency.

Introduction

It is not uncommon for a general practitioner find an elderly patients non-adherent to their iron supplements, because of side effects such as constipation. When it comes to supplements, patients are usually self-medicated and for many reasons they are less compliant with the prescribed dose and dosing frequency [1]. The main goal of this paper is to demonstrate a clinical observation on the use of iron supplements to treat iron deficiency anemia in a patient also suffering from chronic unexplained leukopenia.

Leukopenia is an abnormal reduction in the number of circulating white blood cells, namely granulocytes. Neutropenia is a more specific term referring to the abnormal reduction in the number of circulating neutrophils [2], which is the focus of our case report here. Neutropenia occurs when there is a reduction in the number of produced neutrophils or as a result of their increased destruction, or both. Infection, drugs, malignancy, megaloblastosis, hypersplenism and immune-neutropenia are known causes of leukopenia [3]. The primary threat when dealing with neutropenia lies in the increased risk and severity of infection [4].

Case description

A 67-year-old woman is known to have diabetes mellitus, hypertension, hypercholesterolemia, iron deficiency anemia

and unexplained chronic leukopenia. She is also morbidly obese with a body mass index (BMI) of 43.4 kg/m^2. This woman has been a closely examined patient in our medical center for about 16 years between the years of 1995 and 2011.

In early July, 2011 she was receiving the following medications: Metformin 850 mg/Day, aspirin 100 mg/Day, amlodipine 5 mg/Day, simvastatin 20 mg/Day, ferrous fumarate 100 mg/Day, omeprazole 20 mg/Day. The patient was relatively considered compliant to her medications except for her iron treatment where she only received one 100 mg tablet once or twice a week instead of daily. This was attributed to the accompanying side effects which she complained about when receiving the iron treatment. These side effects included bloating, epigastric pain and constipation. The patient refused to receive iron intravenously against medical advice.

During her 16 year follow up, this patient was consistently found to have unexplained persistent leukopenia. There was no family history of similar conditions and there was no medical history of recurrent infections. She was compliant with taking her daily aspirin pill but had no history of other NSAID use. Her White Blood Cell (WBC) count was continuously in the range of 1,600–3,300 cells/μL (Reference range 4,500–11,000 cells/μL). With over 80 documented separate complete blood count (CBC) tests carried out throughout this 16 year period her WBC was mostly around 2,000 cells/μL. Neutrophil count was typically between 40 and 50 % which is just slightly below average range (52–68 %). Hemoglobin (Hb) level was continually at the lower end of normal, ranging between 9.0 and 12.0 g/dL and never exceeding 12 g/dL (Normal Reference range for females: 12.0–15.0 g/dL). Mean corpuscular volume (MCV) was usually found to be between 70 and 85 μm^3 (Reference range 80–100 μm^3) and her ferritin level constantly remained below 15 ng/ml (Reference range 20–300 ng/ml). Her platelet count was continuously between 200×10^3 and 400×10^3 cells/μL (Reference range $150–450 \times 10^3$ cells/μL). While she was receiving medical attention from our center, she had three documented visits to two different hematologists. After undergoing multiple tests, her leukopenia remained unexplained. Blood film showed microcytic hypochromic anemia with moderate neutropenia. In an effort to better understand the patient's condition, many examinations and laboratory tests were performed always resulting in normal values. The parameters evaluated included blood lead level, vitamin B-12 level, folic acid level, ESR, RF, ANA, Hb electrophoresis, serum creatinine, BUN, total bilirubin, direct bilirubin, LDH, ALP, ALT, and AST. An abdominal ultrasound was unremarkable apart from some signs of mild splenomegaly. Since the patient's documented test results demonstrated the same degree of leukopenia for many years without the occurrence of significant infection, it was decided not to do bone marrow biopsy. A form of chronic benign neutropenia (also known as chronic idiopathic neutropenia) was the most likely diagnosis with Feltey's syndrome being a distant possible diagnosis. She underwent two gastroscopies and three colonoscopies throughout this 16 year period with no remarkable findings except for some mild antral gastritis. Her iron deficiency anemia was attributed to nutritional factors with no good compliance to iron treatment.

On July, 17th, 2011 our patient suffered an acute ischemic cerebrovascular accident (CVA). She developed mild left sided muscle weakness and dysarthria, and was admitted to hospital for two and a half months. Her hospital stay was prolonged because her condition required daily physiotherapy, and because her swallowing ability was diminished, she was on many occasions fed using a nasogastric (N/G) tube. She received exactly the same previous oral medications through the N/G tube for her entire hospital stay. The only difference was that she was given oral ferrous sulfate 325 mg tablets twice daily for the whole two and a half months inpatient period. This was the first time our patient had ever received a full course of a proper dose of oral iron treatment which was monitored and administered by the hospital inpatient nursing staff. Strangely enough, she did not complain of constipation and gastric upset while taking the oral iron supplements during her long hospital stay, so we were for the first time able to observe the consequence of adequate iron supplementation treatment.

The patient was discharged early October, 2011. She had regained muscle strength and was able to swallow again. The biggest surprise was that her WBC count had returned to normal and was now 7,806 cells/μL, and her Hb level had also normalized at 13.7 g/dL. Other CBC indices were within normal range and ferritin level was 122 ng/ml. Patient continued to have normal blood indices for up to 7 months following hospital discharge. Unfortunately, there was lack of follow-up after that. Table 1 below summarizes the ordered laboratory parameters and their values before and after inpatient stay.

Discussion

The persistently low serum ferritin level throughout the preceding years reflects her chronic iron depletion status. The iron deficiency anemia from which our patient was suffering was clearly evident from the low Hb, low MCV, low MCH, low MCHC, low serum iron, high transferrin concentration, low transferrin saturation and low ferritin level. Other causes of microcytic hypochromic anemia such as thalassemia and lead poisoning were excluded by the other tests such as normal Hb electrophoresis and normal lead level, respectively.

Table 1 Patients laboratory parameters

Measured parameter	Unit	Before admission and iron Rx. (July/10/2011)	After discharge and iron Rx. (Oct/11/2011)	Reference range
Hb	g/dL	11.2	13.7	12.0–15.5
WBC	Cells/μL	2,213	7,806	4–11,000
Neutrophil	%	42	54	52–68
Lymphocyte	%	39	37	24–44
Monocyte	%	5	4	3–6
Eosinophil	%	2	1	0–3
Basophil	%	1	1	0–1
Absolute neutrophil count (ANC)	Cells/μL	924	4,212	>1,500
Platelet	Cells/μL	384×10^3	226×10^3	$100–450 \times 10^3$
MCV	fL	73	88	78–96
MCH	pg	22	28	26–34
MCHC	g/dL	28	31	31–37
Ferritin	ng/mL	15	122	20–300
Corrected reticulocyte count (RPI)	%	0.66	1.76	1.0–2.0
Transferrin concentration	mg/dL	442	317	204–360
Transferrin saturation	%	8	35	15–50
Serum iron	Mcg/dL	33	112	60–170

Neutropenia, defined as having an absolute neutrophil count (ANC) below 1,500 cells/μL, can be caused by multiple disease processes. It is commonly seen within the clinical setting in patients suffering vitamin B-12 deficiency, patients with bone marrow depression secondary to chemotherapy, and very commonly but in a transient fashion, with patients suffering from common self-limiting upper respiratory tract virus illnesses [4]. Table 2 lists the classification of neutropenia [5].

Vitamin B12 and folate deficiency were ruled out as a cause for neutropenia in our case because of the normal serum levels (Table 1). Congenital causes and transient post infectious causes were not relevant to our case because of documented prior normal CBC profile when the patient was in her late thirties. Also, post infectious neutropenia was excluded as a cause because it is by definition transient with a self-limited course contrary to the chronic nature of our case [4, 6]. Aplastic anemia and myelodysplastic syndrome are usually irreversible and fit neither the clinical picture, with regards to the long sub clinical medical history (16 years), nor the blood indices findings and blood film results. Post-chemotherapy and drug induced neutropenia's are also ruled out by the patient's medical history.

Clinically relevant causes of neutropenia that should be considered in our case are autoimmune neutropenia and chronic idiopathic neutropenia. Unfortunately our patient did not have testing for anti-neutrophil antibodies (Abs) to rule out autoimmune neutropenia, but the absence of other known autoimmune diseases makes us more confident that this case can be classified as chronic idiopathic neutropenia. This disorder mainly affects middle-aged women with a female: male ratio of 3–6:1 and a median age at diagnosis of 50.5 years. Chronic idiopathic neutropenia usually persists throughout life without major complications [7].

Table 2 Classification of neutropenia

Congenital	Severe infantile agranulocytosis (Kostmann's syndrome), Shwachman–Diamond–Oski syndrome, Myelokathexis/neutropenia with tetraploid nuclei, Cyclic neutropenia,Chediak–Higashi syndrome, Reticular dysgenesis, Dyskeratosis congenita
Acquired	Postinfectious neutropenia
	Drug-induced neutropenia
	Complement activation (haemodialysis, leukapheresis,ARDS)
	Immune neutropenia
	Isoimmune neonatal neutropenia, Alloimmune neutropenia(transfusion reaction), Autoimmune neutropenia(primary), Autoimmune neutropenia(secondary)
	Chronic idiopathic neutropenia
	Hypersplenism
	Nutritional deficiency (vitamin B12 or folate deficiency)
	Diseases affecting the bone marrow
	Postchemotherapy, Aplastic anaemia, Fanconi anaemia, Myelodysplastic syndrome, Acute and chronic leukaemia

Adapted from Capsoni et al. [5]

The significant improvement in the Hb level, WBC and ANC (13.7 g/dL, 7,806 cells/μL and 4,212 cells/μL, respectively) after correcting her iron store status lead us to

believe that the treatment of the chronic iron deficiency anemia with oral iron supplements also treated her 16 yearlong documented chronic idiopathic neutropenia.

Although many maladies have been linked to neutropenia, none conclusively link iron deficiency anemia as a cause. One study found that 2.1 % of patients suffering incidental adulthood neutropenia also had iron deficiency anemia. These patients had an improved neutrophil count when treated with a number of medications including iron supplementation [8]. Another study in India reported a case of an adolescent girl with severe iron deficiency anemia presenting with a clinical picture of pancytopenia [9]. One possible involvement of iron could be its influence on the bone marrow microenvironment regulating myeloid hemopoiesis [10].

Conclusion

As our case suggests, some patients diagnosed with chronic idiopathic neutropenia who clinically present as having unexplained chronic neutropenia might actually be suffering from a form of not yet described iron deficiency induced neutropenia. Our findings also propose iron supplement therapy as a possible treatment for this form of neutropenia.

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Conflicts of interest Each author states no conflict of interest.

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