

Case Report

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Pancytopenia in the context of hypothyroidism and B12 deficiency: A case report and review literature

Background: This case of pancytopenia due to hypothyroidism and B12 deficiency is rare and severe as a reminder that, upon diagnosis of pancytopenia, endocrine disorders such as secondary thyroid hormone deficiency may need to be considered as a potential cause.

Case Presentation: A 38-year-old male presented with progressive weakness, lethargy, and anorexia. Initial labs revealed severe pancytopenia, prompting a hematological workup. Bone marrow aspiration ruled out acute leukemia. Further investigations identified severe primary hypothyroidism (TSH: 200 mIU/L) and vitamin B12 deficiency as the underlying causes, after excluding other common etiologies. Treatment with levothyroxine and vitamin B12 was initiated. The patient showed a rapid and significant hematological response, with all cell lines improving and approaching normal ranges on follow-up, confirming the diagnosis.

Conclusion: In this patient, after the diagnosis of hypothyroidism and receiving levothyroxine, we saw a better stability of the improvement of the patient's symptoms and a further improvement in the number of any blood cell lines chiefly platelet which is one of the regulators of the coagulation pathway, and its deficiency increase the risk of bleeding.

Keywords: pancytopenia, anemia, hypothyroidism, levothyroxine, vitamin B12.

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Hypothyroidism can affect any part of body, including the bone marrow, and the common form of this involvement is normocytic normochromic anemia. Anemia in hypothyroidism is the result of bone marrow depression, vitamin B12 deficiency, folate deficiency or decreased erythropoietin production (1). Actually, thyroid hormones induce the expression of erythropoietin gene by increasing the accumulation of hypoxia-inducible factor1 (2). Therefore, it is expected that the number of red blood cell and hemoglobin will decrease due to reduce of thyroid hormone levels. A reduction in thyroid stimulating hormone in hypothyroidism can cause a decrease in the number of platelets in the blood stream due to the increase in the time required for the release of megakaryocytes from the bone marrow and fragmentation. In fact, the decrease in the number of platelets occurs indirectly and with the effect of thyroid hormones on megakaryocytes (3). Vitamin B12 deficiency can also occur in the context of malabsorption caused by hypothyroidism. At all pancytopenia is more often seen in Grave's disease or autoimmune thyroiditis, although it can also be rarely seen in severe primary hypothyroidism. We report a case with a severe reduction in the number of blood cell groups and hemoglobin in the context of latent hypothyroidism and vitamin B12 deficiency that responded well to combination therapy with levothyroxine and vitamin B12.

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Case Presentation

A 38-year-old male patient, without any underlying disease, referred to a gastroenterologist on July 29, 2023, complaining of weakness, lethargy, anorexia, and vague epigastric pain. In the complete blood count requested by the gastroenterologist, pancytopenia was reported with Hemoglobin (HB)=7 gr/dL (normal=13-17 gr/dL), Platelet (PLT)=112000/uL (normal=150000-450000/uL), White blood cell count(WBC)=2700/uL (normal=4000-11000/uL) and mean corpuscular volume (MCV)=90fl (normal=80-100fl) also the patient was referred to a hematologist. Due to pancytopenia with suspected acute leukemia, the patient underwent bone marrow aspiration.

After 48 hours of bone marrow aspiration, due to progressive weakness and lethargy, the patient was hospitalized for resuscitation and further examination. At

the same time as the patient was hospitalized, the normal flow cytometry of bone marrow aspiration ruled out acute lymphoid leukemia and acute myeloid leukemia. In the observation of aspirated bone marrow under the microscope, erythroid hyperplasia, megaloid changes, pancytopenia, and dysplastic neutrophils, which did not have significant hypersegmentation was seen which was also confirmed by the pathologist (figure 1). After ruling out of acute lymphoid leukemia and acute myeloid leukemia, other causes of pancytopenia such as copper deficiency, hypothyroidism, folate and B12 deficiency, lymphoproliferative diseases, hemolytic anemia and myelodysplastic syndromes were investigated in the patient. According to the existing doubts for the main cause of pancytopenia, tests were requested, which are available in the table below (table1).

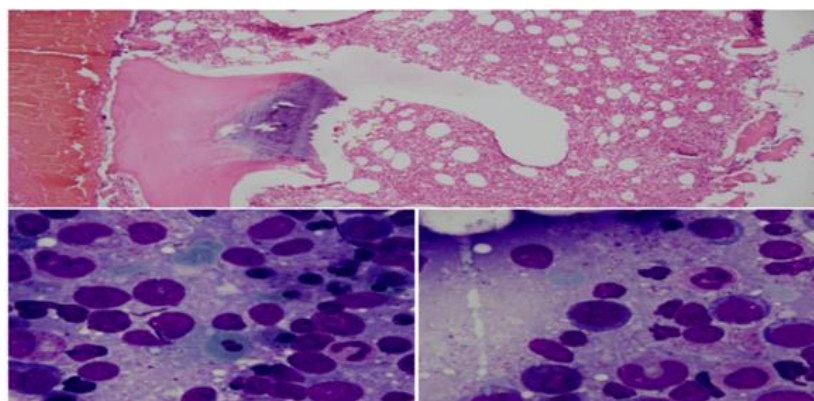


Figure 1. According to the above pictures, acute lymphoid leukemia and acute myeloid leukemia was ruled out by the pathologist for this patient who presented with pancytopenia and fatigue.

Table 1. The following tests have been requested during hospitalization according to clinical suspicions

Cause of pancytopenia	Laboratory values
Copper deficiency	Urine cu=110ug/dl (normal=70-140ug/dl)
Hypothyroidism	Thyroid stimulating hormone (TSH)=200mIU/L (normal=0.4-4mIU/L)
Folate and B12 deficiency	B12 serum level=110pg/dl (deficiency<200pg/dl) Folate serum level=4.2ng/dl (normal>2.5ng/dl)
Hemolytic anemia	Direct coombs=negative Indirect coombs=negative
Lymphoproliferative diseases	Chest and abdomen and pelvic CT-SCAN=no significant lymphoma was seen

According to the data in the above table, hypothyroidism and vitamin B12 deficiency were confirmed for this patient. On the second day of hospitalization, with a decrease in

hemoglobin level from 6.7 gr/dL to 5.9 gr/dL, one packed cell was prepared for the patient, which brought the hemoglobin level to 6.8 gr/dL. Also, on this day, the patient

developed fever and thrombophlebitis after drawing the angiocath from his hand, and his blood culture was also reported positive. Since the patient developed septicemia and there was a suspicion of staphylococcus aureus, in order to rule out endocarditis,

Transesophageal echo was performed, and vegetation was not found in the heart, and due to septicemia and thrombophlebitis, intravenous meropenem was prescribed to the patient for 14 days. On the third day of hospitalization, due to possible vitamin B12 deficiency, treatment with vitamin B12 was started for the patient, and in order to rule out pernicious anemia, due to vague epigastric pain and suspicion of vitamin B12 deficiency, an endoscopy was performed, and a biopsy was taken from the stomach tissue. No evidence of pernicious anemia was found on histology study.

On the fifth day of hospitalization, during the transfer of the patient to computed tomography (CT-SCAN), the patient was subjected to upward-gaze, which immediately the patient was taken to the bed and by placing the legs upwards, the patient returned to his normal state and there was no need for diazepam injection. It happened to upward gaze without foaming at the mouth and urinary incontinency, the issues of seizure and syncope were raised, and syncope due to heart problems was ruled out with 24-hour-Holter-monitoring. Considering the patient's thrombophlebitis, pancytopenia, high lactate dehydrogenase (LDH), and seizures, a negative coomb's hemolytic anemia was suspected, preferably paroxysmal

nocturnal hemoglobinuria (PNH), while the patient had no history of hematuria. By performing flow cytometry and measuring the level of CD55 and CD59 and PNH was also ruled out for the patient, and also with normal haptoglobin level and its non-decrease, coombs-negative hemolytic anemia was also ruled out too. To rule out seizures caused by cerebral sinus thrombosis, magnetic resonance venography (MRV) was requested, which was found to be free of thrombosis. On the sixth day, according to TSH=200 mUI/L(normal=0.4-4mIU/L) and confirmation of hypothyroidism, levothyroxine tablet was prescribed for the patient and its use was started in this day (table 2).

One day before discharge on August 13, 2023, a peripheral blood smear showed significant hyper-segmented neutrophils, and evidence of Myeloid dysplasia syndrome, which did not match the age of the patient, was not seen. Also, the increase of white blood cell (WBC), red blood cell (RBC), and platelet (PLT) is evident compared to the initial slides of the patient. After discharge, the patient was treated with levothyroxine and Vitamin B12 too and when he visited in the clinic on August 21, 2023, he had complete blood cell test with Platelet (PLT)=394000/uL (normal=150000- 450000/uL), White blood cell count (WBC)=8960/uL(normal=4000-11000/uL), Red blood cell count (RBC)=3.56*10⁶/uL (normal=4.7-6.1 × 10⁶/uL), mean corpuscular volume (MCV)=99fl (normal=80-100fl) and Hemoglobin (HB)=11.2 gr/dL (normal=13-17 gr/dL) was showed levothyroxine and vitamin B12 treatment is sufficient in this patient.

Table 2. The patient's complete blood cell diff (cbc diff) changes during hospitalization and seven days after discharge .

Reference	21 AUG 2023	14 AUG 2023	13 AUG 2023	12 AUG 2023	11 AUG 2023	10 AUG 2023	9 AUG 2023	8 AUG 2023	7 AUG 2023	6 AUG 2023	5 AUG 2023	4 AUG 2023	3 AUG 2023	2 AUG 2023	29 JUL 2023
4000-11000/uL	8960	5500	5400	5300	5400	5100	4700	4200	3700	3100	3400	2800	3200	2700	2700
4.7-6.1 × 10 ⁶ /uL	3.54×10 ⁶	2.7×10 ⁶	2.68×10 ⁶	2.43×10 ⁶	2.55×10 ⁶	2.52×10 ⁶	2.46×10 ⁶	1.97×10 ⁶	1.93×10 ⁶	2.22×10 ⁶	2.04×10 ⁶	1.8×10 ⁶	1.57×10 ⁶	1.6×10 ⁶	1.62×10 ⁶
150000-450000/uL	394000	402000	381000	340000	311000	246000	208000	109000	50000	104000	101000	100000	103000	100000	107000
Hb>13 gr/dL	11.2	8.8	8.8	8	8.2	8.8	8	6.9	7.3	8.1	7.5	6.8	5.9	6.7	7

Reference	80-100H	135-225U/L		
21 AUG 2023	99	1114		
14 AUG 2023	103			
13 AUG 2023	105			
12 AUG 2023	105	2648		
11 AUG 2023	104			
10 AUG 2023	105			
9 AUG 2023	110	3958		
8 AUG 2023	112	5250		
7 AUG 2023	114			Start treatment of levothyroxine
6 AUG 2023	112	6550		
5 AUG 2023	113	8104		
4 AUG 2023	116		Start treatment of vitamin B12	
3 AUG 2023	122	7300		
2 AUG 2023	116	4854		
29 JUL 2023	90			
	Mean corpuscular volume (MCV)	Lactate dehydrogenase (LDH)	Order of vitamin B12	Order of levothyroxine

Discussion

The most common hematological problem in hypothyroidism is normocytic normochromic anemia. In fewer cases, it can become microcytic or macrocytic anemia, which may occur due to hypothyroidism coinciding with another hematological issue, such as iron deficiency. In some cases, hypothyroidism can also cause pancytopenia, although the mechanism is not clear. The simultaneous occurrence of vitamin B12 deficiency, normocytic anemia, pancytopenia in the context of primary hypothyroidism is a very rare event that occurred in this case. In hypothyroid patients, anemia can occur due to several factors, including decreased erythropoietin levels, reduced levels of vitamin B12 and folate, and bone marrow suppression (1).

Anemia in context of primary hypothyroidism is often normocytic normochromic anemia but this problem can manifest as macrocytic or microcytic anemia (1, 4). Microcytic anemia is associated with malabsorption of iron and macrocytic anemia is usually associated with B12 deficiency in primary hypothyroid patient (5). In hypothyroidism, the production of all three main blood lines is affected and can cause pancytopenia, the mechanism of pancytopenia in hypothyroidism is not clear (6).

Of course, in the studies conducted in the past, thyroid hormones are considered as an endogenous signal for erythropoietin, and its deficiency affects the number of red blood cell (7). In addition to pancytopenia, hemolytic

anemia can also occur in the context of hypothyroidism. Hypothyroidism can cause disturbances in red blood cell membrane lipids, such as increased phosphatidylcholine and free cholesterol, which can be a main cause of hemolysis in these patient (8). In a case series by Muzammil Khan pancytopenia in context of hypothyroidism, it was suggested that thyroid hormone deficiency was the main cause of pancytopenia. After thyroid hormone replacement, they reported normalization of blood cell lines (6).

In a case series by Dianna Lang B.Sc. pancytopenia in context of hypothyroidism due to panhypopituitarism, they are used oral levothyroxine and prednisone combined treatment to resolve pancytopenia in a 60- year-old man (9). It seems the lack of hormones that are under the control of the pituitary gland can cause pancytopenia with a mechanism that is not completely clear at the moment (table 3).

In this patient, treatment with vitamin B12 was started before levothyroxine administration, but the disappearance of patient's symptoms and the faster increase in the number of any blood group cells started when we decided to have a combined treatment with vitamin B12 and levothyroxine so we recommend in patients with B12 deficiency who presented with pancytopenia if the pancytopenia is not corrected successfully, suspect other causes of pancytopenia, especially the lack or excess of hormones that are under the control of the pituitary gland such as thyroid

hormones or cortisol deficiency and, upon diagnosis, perform the successful treatment of pancytopenia.

In this patient, after the diagnosis of hypothyroidism and receiving levothyroxine, we saw a better stability of the

improvement of the patient's symptoms and a further improvement in the number of any blood cell lines chiefly platelet which is one of the regulators of the coagulation pathway, and its deficiency increase the risk of bleeding.

Table 3. Reported of pancytopenia in the setting of hypothyroidism with their presentations and their treatment effect

Author	Age/Gender	Cell counts in admission	Reference values	Treatment	Fallow-up
Current case	38/Male	HB =7gr/dl WBC =2700/uL PLT=112000/uL	HB=13-17gr/dl WBC=4000-11000/uL PLT=150000-400000/uL	Oral levothyroxine + Vitamin B12	Platelet and White blood cell count were normal after seven days after discharge from hospital
Muzammil Khan (6)	68/Female	HB =9gr/dl WBC =4850/uL PLT =102000/uL	HB=12.1-15.1gr/dl WBC =4500-11000/uL PLT=150000-400000/UI	Oral levothyroxine	Improvement of cell lines within one week of treatment
Samanta et al. (10)	14/Male	HB =6.8gr/dl WBC =2200/uL PLT =110000/uL	HB=13.8-17.2gr/dl WBC=4500-11000/uL PLT=150000-400000/UI	Oral levothyroxine	Improvement of pancytopenia within two weeks and resolution in six weeks
Dianna Lang B.Sc. (9)	60/Male	HB =6.8gr/dl WBC=2200/uL PLT=110000/UI	HB=13.5-17.5gr/dl WBC=4500-11000/uL PLT=150000-400000/UI	Oral levothyroxine + Prednisone	Improvement of pancytopenia within two months after discharge

Hemoglobin (HB), White blood cell count (WBC), Platelet (PLT)

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Consent for publication: The case report was written with the patient's consent while maintaining their confidentiality.

Authors' contribution: All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work

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