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An unusual case of Pancytopenia with Neuropsychiatric disturbances - a case report.

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Abstract:
A 48 years old female presented to the emergency department with shortness of breath. She also reported leg swelling, yellowish discoloration of eyes, and easy fatigability for the past month. Upon physical examination, she was found to be lethargic, dyspnoeic, pale with bilateral pedal edema, and altered mental status. She had a pulse rate of 110/min and a BP of 90/60mmHg. Crepitations were heard bilaterally at the base of the lungs. She was treated for heart failure and her hemodynamic status was stabilized. Meanwhile, routine investigations revealed pancytopenia with a reticulocyte count of 0.2%. Further investigations including bone marrow biopsy were ordered to evaluate pancytopenia. However, determining the cause of pancytopenia remained a diagnostic challenge. The patient's husband provided a history of chronic constipation and frequent mood disturbances in the patient. The history of neuropsychiatric disturbances and persistent bradycardia which the patient had after correction of anemia made us suspect thyroid dysfunction. The thyroid panel showed severe hypothyroidism. Further workup including Anti-TPO antibodies and USG-guided biopsy confirmed the diagnosis of Hashimoto's thyroiditis. Thyroxine supplementation (T.Eltroxine 100 µg) was immediately started. The patient's condition started to improve dramatically, including her mental and hematological status. Pancytopenia, secondary to Hashimoto's thyroiditis, is very rare. Such atypical presentation often causes diagnostic confusion which leads to delayed treatment and a high likelihood of increased morbidity. The frequency of misdiagnosis and the potential for poor prognosis point to the importance of a high degree of suspicion of thyroid dysfunction in patients with unexplained pancytopenia. A picture of neuropsychiatric disturbances with pancytopenia must always prompt one to suspect hypothyroidism.

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I. Introduction

Pancytopenia is commonly attributed to hematological disorders, infectious diseases, nutritional deficiencies, or medications. Therefore, the investigations are often limited to hemogram, ANA profile, and bone marrow study. One of these usually helps us to clinch the diagnosis. Here, we present an unusual case of pancytopenia with associated neuropsychiatric symptoms, secondary to autoimmune thyroiditis in which the above investigations did not turn out to be useful.

II. Case Report

A 48 years old female presented to the emergency department with shortness of breath. She also reported leg swelling, yellowish discoloration of eyes, and easy fatigability for the past month. She had no co-morbidities. She was not an alcoholic/smoker. Upon general examination, she appeared confused, lethargic, dyspnoeic, and had pallor, bilateral pedal edema, and glossitis. Vital examination showed pulse rate= 110/min and BP= 90/60mmHg. Auscultation revealed basal crepitations bilaterally at the base of the lungs. As her symptoms pointed to heart failure, nasal oxygen, and injection furosemide were started immediately. The patient got symptomatically better apart from mildly altered mental status.

Meanwhile, routine investigations were performed and the findings are listed below.

Table no 1: Complete blood count

Hemoglobin	8.5 g/dl
RBC	3.0 million/mm3
HCT	30%
MCV	142.1 fL
MCHC	35.2 g/dl
WBC	3500 cells/mm3
Neutrophils	45%
Lymphocytes	5.7%
Platelet count	95,000 cells/mm3
Manual platelet count	1.0 lakh cells/mm3

Table no 2: Renal function test

Random blood sugar	99 mg/dl
Urea	18 mg/dl
Creatinine	0.6 mg/dl
Sodium	133 mEq/L
Potassium	4.0 mEq/L

Table no 3: Liver function test

Serum bilirubin Direct Indirect	0.7 mg/dl 0.2 mg/dl 0.5 mg/dl
SGOT	32 U/L
SGPT	24 U/L
Serum ALP	61 U/L
Total protein	6.0 g/dl
Albumin	3.0 g/dl
Globulin	3.0 g/dl

Table no 4: other investigations

HIV	Non-reactive
Chest Xray	Features suggestive of pulmonary edema

The routine investigations revealed pancytopenia with dimorphic anemia and a reticulocyte count of 0.2%.

The following investigations were ordered to evaluate pancytopenia but the test reports were unremarkable

Table no 5

Direct Coombs test	Negative
ANA	Negative
Serum Vit. B12	900 pg/ml
Serum folate	5 ng/ml
CT chest	cardiomegaly
CT abdomen	Normal
Echocardiography	EF: 60%, no regional wall motion

	abnormalities

A bone marrow biopsy was performed which showed a cellular marrow with erythroid hyperplasia. Retrospective history from the husband revealed that the patient had chronic constipation and frequent mood disturbances. Moreover, the patient had persistent bradycardia after correction of anemia which along with the neuropsychiatric disturbances prompted us to look for thyroid dysfunction. Hematologist and endocrinologist opinions were sought and the following investigations were ordered.

Table no 6

T3 T4 TSH	25.0 ng/dL 1.66 µg/dL 28.38 µU/mL
Thyroid peroxidase antibody	145.1 IU/ml
Serum cortisol Serum ACTH	8 µg/dL 39.4 pg/ml
Anti intrinsic factor antibody	Negative

Early morning cortisol and ACTH were within normal limits. The patient had severe hypothyroidism. Anti-TPO antibodies were markedly elevated. USG neck showed evidence of thyroiditis. USG guided biopsy revealed lymphocytic thyroiditis. The patient was thus diagnosed to have Hashimoto's thyroiditis/lymphocytic thyroiditis. Thyroxine supplementation (T.Eltroxine 100 µg) was immediately started and packed RBCs were transfused. Her mental status and pancytopenia got improved. Serial follow-up for screening for the development of papillary carcinoma of the thyroid was also done.

III. Discussion

Pancytopenia is the simultaneous presence of anemia, leucopenia, and thrombocytopenia [1]**. N**ew-onset pancytopenia can be caused by a wide variety of etiologies, thus determining the cause is often difficult. These etiologies range from congenital and acquired bone marrow failure syndromes, marrow space-occupying lesions, peripheral destruction of hematopoietic cells, autoimmune disorders, infection, and ineffective marrow production [2]. Although bone marrow examination reveals the underlying cause in most cases, pancytopenia secondary to autoimmune thyroiditis can pose a diagnostic challenge.

Hashimoto's thyroiditis is the most common autoimmune thyroid disease and the commonest cause of hypothyroidism [3]. The hallmark of diagnosis is the presence of thyroid peroxidase(TPO) autoantibodies [4]. Not every patient with hypothyroidism will have all the cardinal symptoms and signs. Pancytopenia can be the presenting feature. In this patient, pancytopenia was diagnosed earlier, which along with the neuropsychiatric symptoms led to the diagnosis of severe hypothyroidism.

Pancytopenia is a rare complication of endocrinopathies. The most common hematologic abnormality associated with hypothyroidism is normochromic normocytic anemia [5]. The exact mechanism of pancytopenia is unclear but it has been suggested that an autoimmune reaction against the bone marrow is the underlying cause [6]. There were prior reports of pancytopenia in patients with autoimmune thyroiditis, but they were usually accompanied by hypopituitarism [7], adrenal insufficiency [8], or pernicious anemia (especially in autoimmune polyglandular syndromes). Unlike those cases, this patient's diagnostics revealed no evidence of any other endocrine abnormalities.

Bone marrow failure secondary to hypotension was also considered but the patient's normal serum lactate levels suggested against this. This lack of lactate production may be explained by decreased tissue metabolic demand secondary to decreased thyroid hormone [9].

Thyroid dysfunction in adults is commonly associated with a host of cognitive and psychiatric problems ranging from altered cognitive function, depression, disorientation, memory impairment, dementia, auditory distortions, psychomotor retardation, and psychosis [10]. However, most patients achieve symptom resolution with levothyroxine replacement therapy [11]. Therefore, early diagnosis and treatment are crucial. The pathophysiology of the thyroid hormone-related changes in the cerebral tissue is diverse and includes changes in neurotransmission, alterations in neuronal or glial cell gene expression, blood-brain barrier dysfunction, increased risk of cerebrovascular disease, and cerebral inflammatory disease [12].

If the patient with altered mental status and positive anti-TPO antibodies doesn't improve with thyroid hormone replacement, then Hashimoto encephalopathy – a feared complication must be considered. It often resolves with corticosteroids.

All patients with hypothyroidism need not have typical clinical features. In this patient, bradycardia was masked by severe anemia and heart failure. After resolution of heart failure patient had persistent

bradycardia which along with the neuropsychiatric symptoms pointed towards hypothyroidism. The thyroid function tests, the level of anti-thyroid peroxidase antibodies, and biopsy showing thyroiditis confirmed the diagnosis of autoimmune thyroiditis.

Hypothyroidism, presenting with classic symptoms is easily diagnosed and treated. However, atypical presentations such as seen in this patient make the diagnosis less apparent and divert the focus of attention towards investigating for other diseases. Moreover, autoimmune thyroiditis as a primary cause of pancytopenia is very rare. If left untreated, severe hypothyroidism can lead to serious complications including myxoedema coma, encephalopathy, and heart failure apart from the complications from pancytopenia. Therefore, timely identification of these atypical presentations is very crucial for prognosis.

In conclusion, we can say that a systematic endocrine workup (thyroid function tests including anti-thyroid peroxidase antibodies, etc) should be part of the standard diagnostic workup of unexplained pancytopenia

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