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Case Report

Generalized edema on a hypothyroid patient with incorrect use of levothyroxine

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ABSTRACT

Hypothyroidism is manifested when thyroid hormone isn't enough for body's requirement and is usually diagnosed by high levels of TSH and low levels of fT4. Generalized edema is commonly associated with cardiovascular, hepatic, or renal diseases and is quite uncommon to see in hypothyroidism; the edema is usually generalized when the disease is severe. Generalized edema in hypothyroidism is traditionally accompanied with more serious hypothyroid symptoms, which is not the case here. It is discussed why the other common causes of generalized edema such as heart failure, advanced kidney disease, nephrotic syndrome, and cirrhosis do not fit here. And we emphasize the importance of thyroid hormone and drug use evaluation. In our case, a 60-year-old man comes with chief complaint of generalized swelling of his body and weakness that slowly worsening. He presents with extremely high blood pressure and generalized edema but with otherwise normal findings. From the labs there is high TSH and low ft4. He was then admitted and given supportive treatment. His levothyroxine was adjusted and he was reeducated for his wrong levothyroxine use, which he took after meal. He was then slowly improving and was discharged.

Keyword: Generalized edema, Hypothyroidism, Levothyroxine

INTRODUCTION

Hypothyroidism results from low thyroid hormone that isn't enough for the body requirement. It is usually diagnosed by lab findings in which showed high levels of TSH and low levels of fT4. The presentation can vary from asymptomatic to myxedema coma, which is an extreme presentation of this condition.[1] Generalized edema is commonly associated with cardiovascular, hepatic or renal diseases and uncommonly seen in hypothyroidism, called myxedema; which usually presents when the disease is severe.[2] In this paper, we report a patient that comes with generalized edema that has been progressively worse. On evaluation, we didn't find any of the usual suspect of generalized edema except for uncontrolled hypothyroidism. We suspect it was the cause and after treatment, the edema is slowly subsiding. With this paper we present another cause of generalized edema which is hypothyroidism.

CASE REPORT

A 60-year-old man comes to the emergency department with chief complaint of generalized swelling of his body for one to two months now. He also complained of feeling weak that worsened yesterday. He has been going to several doctors before for his swelling complaint but he has not felt any significant improvement even though he was given diuretics. Initially, he complaints of swelling at both of his legs, then slowly started to feel swelling at other extremities. He also said to have very little appetite. He presents with 209/108 mmHg blood pressure, 66 times/min heart rate with normal temperature and respiration rate. His body weight is 70 kg with 170 cm in

height. Previous medical history is notable of hypertension which is controlled with once daily 8 mg candesartan and diabetes which is controlled by long and rapid acting insulin, which the patient discontinued as a result from lowered appetite. 16 mg of candesartan and 10 mg of amlodipine was administered for the high blood pressure. He was admitted for further monitoring. On physical examination there is edema on all extremities, which is non-pitting in nature and felt dense when palpated. Other physical exams don't give any significant information. The lung is clear on auscultation. The cardiologist then gives furosemide iv for the edema.

RESULTS

From the laboratory results, routine complete blood count is normal, blood glucose is normal but on the low side, normal urea but with a slightly elevated creatinine. Creatinine result is similar to the lab result obtained in 2022 before thyroidectomy. ALT and AST are slightly elevated with normal electrolyte panel and albumin. The complete blood results can be seen at Table 1. On chest x-ray there is no any significant abnormalities except for cardiomegaly which is shown in Figure 1.

Echocardiography was performed and it didn't reveal any heart structure abnormalities. Then, endocrinologist was consulted because of the unresolved hypothyroidism from his total thyroidectomy at 2022, even though once daily levothyroxine was administered. The thyroid function test was shown at the table below.

Table 1: Laboratory results.

Labs	Results	Reference
Leukocyte	5.10	4.0-10.0
Hemoglobin	13.7	13.0-18.0
Hematocrit	41.4	40.0-54.0
Thrombocyte	186	150-400
Blood glucose	84	80-200
ALT	47 U/l	0-42
AST	108 U/l	0-37
Free T4	<0.40	0.70-1.48
TSHs	40.1281	0.3500-4.9400
Urea	35 mg/dl	10-50
Creatinine	1.6 mg/dl	0.3-1.2
Sodium	139 mmol/l	130-145
Potassium	3.8 mmol/l	3.5-5.5
Chloride	99 mmol/l	95-108
Albumin	4.3 g/dl	3.8-5.1
HbA1c	6.9 %	Diabetes≥6.5
ESR	11 mm	0-10

On evaluation, the swelling still persists even though furosemide was given regularly. On further questioning, it is revealed that he usually took levothyroxine after dinner. He then was re-educated to take levothyroxine at the morning before any meals and may eat at least one hour after levothyroxine was taken. The levothyroxine dose was adjusted to 150 mcg once daily.

On supportive and renewed levothyroxine regiment, the patient starts to feel a little better. With increased appetite, insulin is then restarted at a lower dose. The swelling is also start resolving. After several days without any significant problems, the patient is then discharged to continue follow up on outpatient basis.

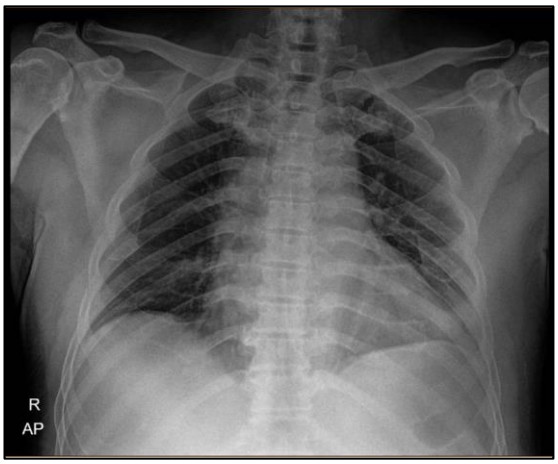

Figure 1. Chest X-ray result.

DISCUSSION

Hypothyroidism happens when thyroid hormone production from the thyroid gland is not adequate or the stimulation to the gland from hypothalamus and pineal gland isn't enough. The causes include primary gland failure or secondary causes like surgery, infection or hyperthyroid treatment. Common symptoms include intolerance to cold, increasing weight, dry skins, fatigue, constipation and change in voice. The signs and symptoms that lead to thyroid dysfunction is usually nonspecific and non-diagnostic, especially on the early stage of the disease. So, the diagnosis of hypothyroid is usually based on high levels of thyroid-stimulating hormone (TSH) and lowered free thyroxine (fT4) levels in the circulation.[3] In this patient, the cause of hypothyroidism is thyroidectomy surgery and he present with high TSH and low fT4 which indicates that his hypothyroidism isn't controlled well by levothyroxine treatment.

Myxedema means edema of the skin and soft tissue, which is caused by accumulation of interstitial albumin and other proteins, thus leading to excessive interstitial protein. The term itself is most commonly used in the context of hypothyroidism and myxedema coma. Myxedema coma itself usually refer to patient that present with severe hypothyroidism, but sometimes it is a misnomer. Not all patients with severe hypothyroidism have classic nonpitting edema, and not every patient will present in a coma.[4] Our patient comes with generalized non-pitting edema and with the lab result those points to uncontrolled hypothyroidism, we suspect that the edema is caused by it.

The exact pathophysiology of myxedema is still unknown, but there are several insights. Myxedema is caused by suction of plasma filtrate into the tissue spaces as a result of overproduction of interstitial collagen and mucopolysaccharides by fibroblasts. Increased extracellular matrix components augments the elastic recoil of the interstitial gel matrix and produce a highly negative interstitial fluid pressure. As a consequence, lymph flow is reduced and interstitial osmotic pressure is increased. In effect, these changes create a suction force that accelerates fluid filtration and the development of edema. The dermal accumulation of mucopolysaccharides, especially hyaluronic acid and chondroitin sulfate, results in a non-pitting edema due to these molecules' ability to bind water.[5]

Some studies showed increased extravasations of plasma proteins, which usually cause the non-pitting nature of the edema, and with lack of a compensatory increase in lymph flow and protein return rate caused the edema to keep worsen and, in some cases, resulted in accumulation of fluids in pleural, peritoneal or pericardial cavities. Lange demonstrated that in hypothyroidism state, capillary permeability increased with the leakage of plasma proteins and the permeability rapidly returned to normal with thyroid hormone therapy, which may explain the relatively quick decrease of edema in our patient. Vascular endothelial growth factor (VEGF) was thought to be implicated in the course of pathogenesis in hypothyroid induced edema, but still need more studies to confirm it. VEGF is produced by thyroid follicular epithelial cells in response to the stimulation of TSH receptor, which leads to increase in vascular permeability and subsequently edema.[6] Causes of generalized edema is usually from decompensated heart failure, decompensated cirrhosis or kidney failure. In heart failure patients, edema usually accompanied with other signs of heart failure. In this patient we don't find any signs and symptoms like orthopnea, paroxysmal nocturnal dyspnea, dyspnea on effort, S3 heart sound and pulmonary rales.[7] Even though he has cardiomegaly as the chest x-ray suggest, there is no other heart failure signs and echocardiography comes out normal. And he also has been given furosemide before with no significant improvement of the swelling. Edema in cirrhosis patients usually presents with ascites in addition to some or generalized edema. In cirrhosis patient, albumin production is impaired causing hypoalbuminemia that play a part in causing edema. Decreased albumin in circulation will cause lowered oncotic pressure that made fluids move to interstitial spaces.[8] In this patient, he only has a slight increase in ALT and AST and with normal albumin, we can presume that he still has a normal hepatic function. In addition, we don't find other hepatic cirrhosis signs such as jaundice, palmar erythema, spider nevi and ascites.

Even though this patient has elevated creatinine, we don't think it is high enough to indicate severe kidney failure. And in this patient, we don't see any other signs of chronic kidney disease like anemia, azotemia and decreased urine output. When we calculate his estimated glomerular filtration rate using CKD-EPI 2021 formula, we get 49.0 ml/min/1.73 m^2 which put him in stage III CKD.[9] Even though the edema right now most probably isn't caused by renal abnormalities, he needs to be followed closely to prevent the disease from progressing. From his normal albumin, we ruled out nephrotic syndrome as one of the causes of generalized edema.

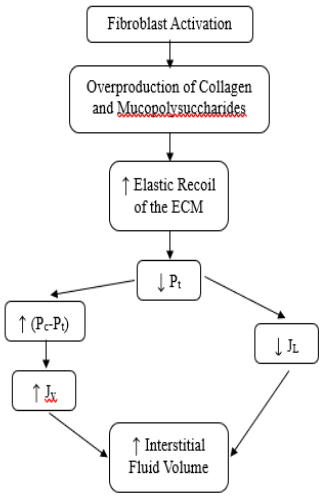

Figure 2: General pathophysiology of myxedema.

As a side note, in this patient we found increased creatinine, which we ruled out as caused by hypothyroidism. It is because of he has elevated creatinine before thyroidectomy, so the renal abnormalities is likely caused by hypertension and diabetes. But there is a study that showed an association between hypothyroidism and lowered glomerular filtration rate. Unfortunately, that study has not revealed the exact mechanism how hypothyroidism causes renal injury but it is thought that it may be related to renin-angiotensin-aldosterone system problems associated with thyroid hormone.[10]

CONCLUSION

In several case reports that we find, usually generalized edema is found on patients who presents with signs of severe hypothyroidism. Some of them have TSH levels of 30 to 190 µIU/ml. Which in this patient, the TSH level is 40 and the edema cannot be explained by other causes. He also improved by proper levothyroxine administration and dose adjustment. So, we conclude that the edema is caused by hypothyroidism.

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