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THE ATYPICAL COMPLICATIONS OF GRAVE'S DISEASE: PANCYTOPENIA, CHRONIC HEPATIC INJURY, AND PULMONARY HYPERTENSION -AN COMPREHENSIVE REVIEW

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REVIEW ARTICLE

ABSTRACT

Graves' disease is an autoimmune disorder that results in hyperthyroidism. In this condition, the thyroid gland produces an excessive amount of thyroid hormone in the body. Graves' disease is a common type of hyperthyroidism in developed countries. It is more common between the ages of 30 and 60, and women are 5-10 times more likely to develop it than men. Every disease is associated with complications that manifest as signs and symptoms. As a result, Graves' disease has a few atypical complications that are difficult to detect. According to research, Grave's disease causes Pancytopenia which is defined as an increase in all three hematologic cell lines. The condition is not a disease in and of itself, but rather a common pathway caused by a variety of different etiologies that can be contagious, autoimmune, hereditary, nutritional, and/or malignant. Also, chronic liver disease is characterized by the progressive deterioration of liver functions. Liver functions include the production of clotting factors and other proteins, detoxification of harmful metabolic products, and bile excretion. This is a continuous process of liver parenchymal inflammation, destruction, and regeneration that leads to fibrosis and cirrhosis. Cirrhosis is the terminal stage of chronic liver disease, characterized by disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and extracellular matrix deposition. The other atypical complication that is commonly found is pulmonary hypertension. High blood pressure in the blood vessels that supply the lungs is referred to as pulmonary hypertension. It is a severe condition that can cause damage to the right side of the heart. The pulmonary artery walls thicken and stiffen, making it difficult for blood to pass through. The reduced blood flow makes the right side of the heart work harder to pump blood through the arteries.

Keywords: Grave's Disease, atypical complications, pancytopenia, chronic hepatic injury, pulmonary hypertension.

INTRODUCTION

An autoimmune disorder termed Graves' disease results in hyperthyroidism. Your thyroid gland produces an excessive amount of thyroid hormone when you have this illness. One of the most prevalent types of hyperthyroidism is Graves' disease. Your immune system produces antibodies called thyroid-stimulating immunoglobulins when you have Graves' disease. The healthy thyroid cells are then adhered to by these antibodies. [1, 2] Your thyroid may produce too much thyroid hormone as a result of these.

Why some people get autoimmune diseases like Graves' disease is a mystery to researchers. These conditions most likely result from an interaction of genes and an exterior trigger, like a virus. Thyroid-stimulating immunoglobulin (TSI), an antibody produced by your immune system in Graves' disease, binds to thyroid cells. Thyroid-stimulating immunoglobulin (TSI), an antibody produced by your immune system in Graves' disease, binds to thyroid cells. Thyroid-stimulating hormone (TSH), a hormone produced in the pituitary gland that instructs the thyroid how much thyroid hormone to produce, is similar to TSI in its action. Your thyroid overproduces thyroid hormone as a result of TSI.

Although it might be indolent or subacute, the beginning of Graves' illness is typically abrupt, indicating the sudden development of stimulatory TSH-receptor antibodies. Patients describe weight loss despite an increased appetite, heat sensitivity, irritability, sleeplessness, sweating, diarrhea, palpitations, muscle weakness, and irregular menstruation as the characteristic signs of hyperthyroidism. Diffuse goiter, fine resting tremor, tachycardia, hyperreflexia, eyelid lag, warm, smooth skin, and proximal myopathy are examples of clinical symptoms. Atrial fibrillation and a thyroid bruit, which both reflect the substantial increase in thyroid vascularity, are less frequent findings.

SIGN AND SYMPTOMS

The autoimmune thyroid disease known as Graves’ disease (GD) is the common contributor to hyperthyroidism, which is the result of the overproduction of thyroid hormones. GD can also demonstrate various kinds of signs and symptoms. The symptoms of GD can be categorized into anatomical regions. Generally, an increase in basal metabolic rate, and losing weight regardless of eating habits are the common symptoms. From the skin aspect, the manifestations include an increase in sweating, pretibial myxedema, alopecia, and vitiligo. Besides, Graves' dermopathy is a rare manifestation of GD that involves the thickening of the skin usually on the shins or the tops of the feet. The eyes aspect includes Graves' ophthalmopathy which involves bulging of the eye(s), redness, retracting and lagging eyelids, sensitivity to lights, double vision, and visual loss. The neck aspect includes enlargement of the thyroid gland (goiter), and thyroid bruits. The chest aspect includes enlargement of breast gland tissue in males (gynecomastia), palpitations, tachypnea, and tachycardia [23]. The GD symptoms involving the extremities aspect include edema, acropachy, and onycholysis of nails. Meanwhile, neurologic signs of GD are such as fine tremors of the hands or fingers, and hyperactive deep tendon reflexes. Moreover, GD can also result in changes in menstrual cycles in women, or erectile dysfunction and reduced libido in men. Diarrhea or frequent bowel movements are also common signs of GD. Psychiatrically, it can cause restlessness, anxiety, irritability, fatigue, sleep disturbance or insomnia, depression, and fatigue. However, the signs and symptoms may vary on the individual and the severity of the GD. The patient experienced breathlessness (dyspnea), palpitations, generalized edema (bilateral pedal edema extending to the lower limbs), diffuse goiter with thyroid bruit, and exophthalmos.

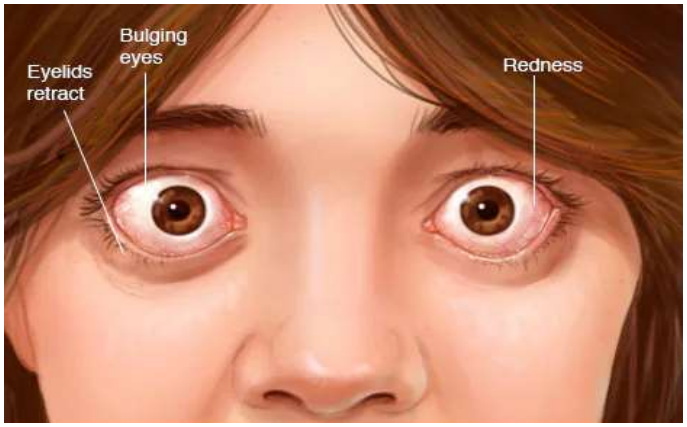

Figure 1: Bulging eyes and redness in the eye

(https://www.mayoclinic.org/diseases-conditions/graves-disease/symptoms-causes/syc-20356240#dialogId43089153)

Based on the reviewed article, the patient was reported with three rare complications of Graves' Disease, which are pancytopenia, chronic hepatic injury, and pulmonary hypertension (PH). Pancytopenia – due to raised bilirubin (mainly direct bilirubin) and alkaline phosphatase (ALP) – can demonstrate symptoms such as fatigue, fast heartbeat (palpitations), fever, pale skin, purple or red spots on the skin, rash, easy bruising, and abnormal bleeding. The patient experienced similar symptoms of pancytopenia and GD such as fatigue and palpitations or fast heartbeat. Then, the chronic hepatic injury may exhibit symptoms like fatigue, nausea, loss of appetite, diarrhea, vomiting blood, blood in the stool, jaundice, disorientation, and fluid buildup in the abdomen and extremities. Fatigue, nausea, and diarrhea are similar symptoms to GD. The patient showed liver impairment with raised bilirubin (mainly direct bilirubin), ALP, and gamma-glutamyl transferase (GGT), indicating the cholestatic pattern of liver injury. Meanwhile, signs and symptoms of PH include dyspnea, tiredness, dizziness, angina, palpitations, and edema in the legs, ankles, feet, or abdomen. Similar symptoms of PH to GD are dyspnea, fatigue, palpitations, and edema. It is reviewed that PH can be found in patients that have GD or nodular goiter associated with hyperthyroidism. The patient had a mild left ventricular which was indicated by bilateral basal lung crepitations, right heart failure, and edema.

ATYPICAL COMPLICATIONS OF GRAVE'S DISEASE

- **Pancytopenia**

Rarely has GD with pancytopenia been described in the literature. Patients with hyperthyroidism are more likely to have single-lineage abnormalities. Anemia, leukopenia, or thrombocytopenia occur in approximately 34%, 5.8%, and 3.3% of hyperthyroid patients, respectively [6, 7, 8]. Anemia in GD is typically chronic disease anemia. The pathogenesis of GD-related pancytopenia is not fully understood, and various theories exist, including (i) high levels of circulating thyroid hormones, resulting in ineffective hematopoiesis; (ii) shortened blood cell lifespan, either by immune destruction or sequestration; (iii) autoimmune mechanisms, given the presence of antineutrophil and antiplatelet antibodies; and (iv) direct bone marrow toxicity, as excessive thyroid hormones [4, 5].

Whatever the pathogenesis, it is recommended that all cases of pancytopenia be evaluated for hyperthyroidism, even if it is not clinically evident in the first instance. The use of antithyroid medications can be a source of concern in the management of patients with GD and pancytopenia. Thionamides are commonly prescribed antithyroid drugs that have been linked to agranulocytosis and aplastic anemia [7, 9, 10]. However, it may be difficult for some GD patients because thioamides are contraindicated in patients with a baseline neutrophil count of 0.5 109/L and should be discontinued if the neutrophil count drops below 1.0 109/L after their initiation. To choose a conservative approach to treatment for this patient, using alternatives such as Lugol's solution and cholestyramine to avoid aggravating the pancytopenia. The use of radioactive iodine during the presentation could have triggered a thyroid storm, so it was not considered.

- **Chronic hepatic injury**

Chronic hepatic injury is when the liver tissue is replaced with scar tissue which results in liver cirrhosis. Based on the reviewed article, the patient was diagnosed with cholestatic liver disease as a complication due to Graves' disease (GD). It is considered a chronic condition of the liver, where there is impairment or blockage to the bile flow. She showed resolution in her hyperthyroid and improvement of ALP and GGT level after treatment with carbimazole for 3 months. This indication then ruled out the association of autoimmune liver disease. The plausible mechanisms or processes of liver damage in hyperthyroidism include liver impairment and cholestasis in the centrilobular liver cells as a result of hypoxia due to decreased oxygen supply; congestive heart failure; excess level of thyroid hormone leading to toxicity; and association with autoimmune liver disease. Cholestasis can demonstrate signs and symptoms such as jaundice to the skin and eyes, skin itches, dark urine, and light-colored and foul-smelling stool. The laboratory findings of cholestatic liver injury are elevated levels of bilirubin, ALP, and GGT. Bilirubin is the yellow pigment, which is the product of the breakdown of hemoglobin. Excess in this pigment will result in entering the bloodstream and accumulating. Since the patient had hyperthyroidism with raised liver enzymes, treatment was challenging. This is because anti-thyroid drugs (ATDs) can cause direct toxicity to the liver [20, 21]. Therefore, alternative treatments are encouraged such as radioactive iodine ablation or thyroidectomy.

- **Pulmonary hypertension**

A wide range of unusual cardiovascular manifestations has been reported in association with hyperthyroidism. Pneumoarterial hypertension (PH), right heart failure, myocardial infarction, and heart block are examples. Clinically, GD may present with isolated right-sided heart failure. The following theories have been proposed to explain the relationship between hyperthyroidism and PH: I autoimmune-mediated endothelial remodeling; (ii) mechanical endothelial damage caused by high cardiac output; (iii) accelerated metabolism of pulmonary vasodilators (nitric oxide and prostacyclin); (iv) inhibited metabolism of pulmonary vasoconstrictors (endothelin-1, serotonin, and thromboxane); and (v) enhanced pulmonary vascular response Thyroid stimulating hormone receptor antibody, pulmonary vascular resistance, and cardiac output have all been found to have a significant linear correlation with pulmonary artery systolic pressure [11, 13, 14, 16]. In terms of treatment, methimazole produced a more rapid improvement in PH. The methimazole effect could be attributed to its ability to suppress Ng-nitro-l-arginine methyl ester production, which acutely inhibits nitric oxide synthesis, resulting in increased nitric oxide levels. Methimazole may also cause direct vasodilation of the pulmonary vasculature. Thyroid dysfunction should be considered in patients with unexplained PH because untreated hyperthyroidism can lead to refractory PH [12,

13, 17]. As a result, once GD treatment is initiated, some patients gain weight, but patients who have complications such as right heart failure and edema will lose weight as they recover. By the time euthyroidism is restored, most cases of PH have recovered.

TREATMENT OF GRAVE'S DISEASE

Graves' disease treatment cannot yet target the cause because it is unknown. When thyrotoxicosis appears to be the primary indication or ophthalmopathy appears to be the more urgent aspect of the disease, control is sought. Treatment options include surgery, medications, and therapy. Antithyroid drugs are widely used for long-term treatment. Approximately one-third of patients who receive long-term antithyroid therapy achieve permanent euthyroidism. In children and young adults, drugs are the preferred initial therapy. A subtotal thyroidectomy is an acceptable form of therapy if an excellent surgeon is available, but it is becoming less common in recent years.

Figure 2: Methimazole
(antithyroid drug)
(https://d3pq5rjvq8yvv1.cloudfront.net/catalog/product/cache/1/image/262x300/9df78eab33525d08d6e5fb8d27136e95/m/e/methimazole_10mg_tablets_generic_tapazole.jpg)

Figure 3: Carbimazole
(antithyroid drug)
(https://5.imimg.com/data5/SELLER/Default/2021/2/RJ/TN/GA/105453881/carbimazole-5mg-tablets-500x500.png)

CONCLUSION

In conclusion, Graves' disease is an autoimmune condition that stimulates the thyroid gland to create thyroid hormones, which results in hyperthyroidism. Establishing a Graves' disease diagnosis can be done by history taking and laboratory testing. Moreover, after one episode, there is a chance that Graves' illness will return, but that chance will gradually decrease. It's crucial to stop smoking right away since it can exacerbate the thyroid eye illness that's connected to this problem. The thyroid will become underactive as a result of surgery and, in many cases, radioiodine, necessitating a lifetime of thyroid hormone replacement therapy (levothyroxine) for the patient. The alternative to radioiodine or surgery is to take an anti-thyroid medication for a long time (up to lifelong). The drawback of this strategy is that people can still experience a Graves disease flare-up.

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