Case Report **Open Access**

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Pseudohyperthyroxinemia in a hypothyroid patient secondary to chronic phlegmon

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Abstract

Background: Elevated free thyroxine could be primary or secondary, endogenous or exogenous and often presents with symptoms of hyperthyroidism. Thyroxine levels are low in hypothyroidism, where the individual requires exogenous supplementation to maintain a euthyroid state. However, thyroxine levels may be elevated in a hypothyroid patient because of over-supplementation/over-suppression with exogenous agent(s) or secondary to other pathologies and rarely, laboratory error or assay interference may cause alteration in the levels of the thyroid hormones.

Case report: A 44-year-old man with well controlled hypothyroidism was referred for assessment of markedly elevated TSH and free thyroxine levels with low free T_3. Clinically the patient was hypothyroid with symptoms of fatigue and weight gain of 30 pounds over the past 3-months and the TSH levels were consistent with marked hypothyroidism. However, free thyrxoine was markedly elevated, opposite of what to be expected. A systematic evaluation, presented here, was helpful in the diagnosis of pseudohyperthyroxinemia secondary to assay interferences in a timely fashion, avoiding unnecessary further investigations.

Conclusions: Interference in immunoassays is an important clinical problem that is underestimated and can have important clinical consequences. It is important to recognize the possibility of such interferences early in the diagnostic process and to implement protocols to identify these whenever possible, in a timely fashion, to prevent untoward consequences. Vigilance by both the clinician and the laboratory staff is important.

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Introduction

Elevated free thyroxine (fT_4) could be primary or secondary, endogenous or exogenous, and often presents with symptoms of hyperthyroidism. The thyroid hormone levels are low in hypothyroidism, where the individual requires exogenous supplementation to maintain a euthyroid state. The fT_4 levels may be elevated in a hypothyroid patients because of over-supplementation/over-suppression with exogenous agent(s) or secondary to other pathologies, e.g. teratoma [1]. Rarely, laboratory error or assay interference because of antibodies [2–5] may cause alteration in the levels of the thyroid hormones. I present a case, where assay interference secondary to heterophile (IgG) antibodies caused marked elevation of fT_4 in a severely hypothyroid patient resulting in discordant thyroid function test results where a systematic evaluation and discussion with the laboratory personnel led to resolution of the issue in a timely fashion, preventing expensive investigations. A systematic approach to assess such discordant thyroid results is presented.

What is known about this topic?

– Antibodies causing interference with immunoassays is known but is underestimated.
– Interference with immunoassays is often considered late in the diagnosis, after extensive unnecessary investigations.

What this case adds?

– A case is presented with severe hypothyroidism and marked hyperthyroxinemia, where a systematic approach avoided unnecessary investigations and led to timely diagnosis and management.
– With the exponential growth of biologics or monoclonal antibodies for different diseases, more and more patients are being exposed to animal proteins, increasing the potential for such antibodies and interferences.
– A strong vigilance by both the clinician and the laboratory staff if required to evaluate discordant results in a timely fashion to avoid unnecessary investigations and untoward consequences.

Case presentation

A 44-year old man with morbid obesity, obstructive sleep apnea and history of hypothyroidism presented with symptoms of progressive tiredness and weight gain of 30 pounds over the past 3-months. The hypothyroidism was well-controlled 16-months prior on L-thyroxine 150 µg a day for 3 years. A year ago, he developed septic shock secondary to streptococcal infection, with multi-organ failure requiring prolonged hospitalization with the development of a large sacral ulcer that healed with the formation of a grape-fruit size phlegmon in the sacral area. Physical examination was unremarkable except for morbid obesity and a soft, non-tender phlegmon in the sacral area. He was noted to have markedly elevated thyroid stimulating hormone (TSH) and fT_4 (Table 1).

Clinically the patient was hypothyroid with symptoms of fatigue and weight gain of 30 pounds over the past 3 months and the TSH levels were consistent with marked hypothyroidism. However, fT_4 was markedly elevated, opposite of what was to be expected. The various possibilities (Table 2) that could cause discordance between TSH and fT_4 were considered. As the patient had previously documented hypothyroidism that was optimally controlled on a stable dose of L-thyroxine, the possibilities of familial dysalbuminemic hyperthyroxinemia (FDH), TSH-secreting pituitary adenoma (TSH-OMA) were felt to be low. Non-adherence to therapy with a recent overdose of L-thyroxine, laboratory error and assay interference were felt to be more likely. A suppressed serum thyroglobulin ruled out endogenous production of thyroxine.

I discussed the possibility of assay interference with laboratory personnel and requested them to analyze the sample using a different assay, for which the laboratory sent the aliquot of the specimen to another laboratory in the area that uses a different assay (2-step assay) and this confirmed the possibility of assay interference, the fT_4 was low as expected at 4.4 pmol/L (Table 1), in keeping with patients clinical symptoms. The diagnosis of pseudohyperthyroxinemia secondary to assay interference was made and the dose of L-thyroxine was increased to 200 µg a day and the TSH and fT4 normalized a few months later. Further assessment revealed markedly elevated serum IgG (Table 1) and a bone marrow ruled out multiple myeloma. The serum immunoelectrophoresis showed this to be polyclonal, consistent with an inflammatory response.

Table 1: Laboratory data over a 2-year period.

			16-Months before	31st October	6th November	11th November	7th January	24th January
Test	**Assay/method**	**Normal range**						
TSH	Siemens	0.55–4.78 mIU/L	4.92	**247.13**	**235.76**	**87.45**	3.69	0.20
Free T_4	Siemens ADVIA Centaur CP[a]	11.5–22.7 pmol/L		**>155**	**145**		**82.8**	
	Ortho VITROS 5600[b]	10.0–28.2 pmol/L			4.4	6.6		21.4
Free T_3	Siemens	3.5–6.5 pmol/L			5.5	5.8		
Thyroglobulin	Roche E602	<60 µg/L		<0.1		<0.1		
Thyrotropin Binding Inibitor (TBII)		<1 IU/L				1.1		
Serum IgG		6.3–14.9 g/L				**34.56**		

[a]1-step assay. [b]2-step assay. The bold values are abnormal values.

Table 2: Differential diagnosis, clinical and laboratory features in individuals with elevated Free T_4 and normal/elevated TSH.

Differential diagnosis	Clinical phenotype	Goiter	TSH	Free T_4	Free T_3	Remarks
Resistance to thyroid hormone (RTH)	Hypothyroid or euthyroid	Yes	Normal or high	High	Normal or low	Central or peripheral, Family history may be present
Pituitary adenoma (TSH-OMA)	Hyperthyroid	Yes	High	High	High	Alpha-subunit of TSH: TSH molar ratio >1
Antibody interference	Hypothyroid or euthyroid	May be present	High or normal	High	Normal or low	Autoantibodies or heterophile antibodies present
Defective selenoprotein synthesis-SBP2 gene mutation	Euthyroid	No	Normal or slightly high	High	low	Often recessive
Exogenous thyroid hormone ingestion	Variable	No	Low, normal or high	High	Normal or high	Low serum thyroglobulin

Discussion

Thyroid hormones (T_4 and T_3) bind reversibly to one of the three plasma proteins – thyroxine binding globulin (TBG), transthyretin, and albumin. About 99.97% of T_4 and 99.7% of T_3 are bound to these proteins. The remainder of these hormones is the hormonally active free hormone circulating in the blood. The levels of the binding proteins are affected by excess estrogens (pregnancy, use of oral contraceptives, hormone replacement therapy, tamoxifen or raloxifen) or medications (5-fluorouracil, clofibrate and opiates) or disease states (hepatitis). Assays for the measurement of the total amount of these hormones are affected by the changes in the levels of these binding proteins. However, assays of circulating free thyroid hormones are not affected by the changes in the levels of binding proteins and these are now routinely used in clinical practice.

Resistance to thyroid hormone (RTH) is uncommon and, as the name implies, is characterized by reduced responsiveness of the target tissues to thyroid hormones. Biochemically, the picture is similar with elevated fT_4 and non-suppressed TSH, suggesting resistance to thyroid hormone action in the hypothalamic-pituitary axis. This was considered but the serum immunoglobulins which may be low in RTH, were elevated in this individual. The past history of hypothyroidism and under optimal control and stable until 16-months ago, as well as normal fT_3 suggests low likelihood of this.

TSH-secreting pituitary adenoma (TSH-OMA) causing secondary hyperthyroidism was less likely in view of suppressed thyroglobulin levels ruling out an endogenous cause of increased thyroid hormone production, past history (although it may occur at any time), and a low fT_4 when measured by different assay.

The suppressed levels of serum thyroglobulin may occur with the absence of thyroid tissue (after total thyroidectomy, or thyroid atrophy with almost no functional thyroid tissue) or with exogenous thyroid supplementation [6–8]. Markedly elevated TSH was consistent with the clinical diagnosis of hypothyroidism and suppressed serum thyroglobulin suggests either complete absence of thyroid tissue or exogenous administration of thyroid hormone. This further suggests that the patient was taking the medication, although the dose may not have been sufficient to optimally suppress TSH. A simplified approach is presented in Figure 1.

Different laboratories use different assays/reagents to determine various biochemical tests that may result in variations in results from one laboratory to another. For thyroid hormone assays some laboratories use a two-step [9] assay while others use one-step assay [10, 11]. In this individual, the measurement of fT_4 by one-step assay (Siemens ADVIA Centaur CP) was significantly higher than the two-step (Ortho VITROS 5600) assay. However, such interferences are often unpredictable and can occur with either of the assays, being primarily dependent on the nature of the interfering antibody [12].

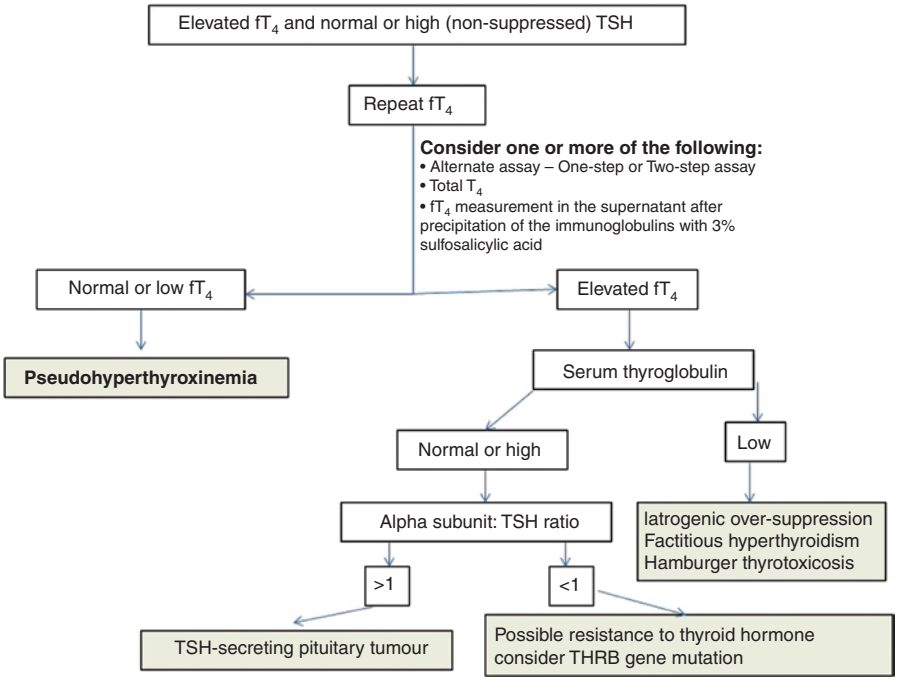

Figure 1: Approach to a patient with hyperthyroxinemia and non-suppressed TSH.

Interference in immunoassays is serious but often unrecognized [13]. Interference can be analyte dependent or independent and may increase or decrease the measured result. Analyte-dependent interferences in the immunoassays are caused by the interactions between the component of the sample with one or more reagent antibodies. These could be heterophile antibodies, human anti-animal antibodies (HAAA), rheumatoid factor and other endogenous antibodies that can occur both in health and disease. Autoantibodies against thyroid hormones have been decribed in patients with Hashimoto's thyroditis, Graves' disease, goiter, thyroid cancer and different autoimunne disease. Antibody prevalence is variable and may be as high as 10% in patients with autoimmune disease, although only a minority of such samples demonstrate clinically significant assay intereference [14]. These can be any of the IgG, IgA or IgM class, and polyclonal or monoclonal. These different type of antibodies can bridge the assay antibodies together resulting in false positive or negative results [12, 15, 16]. The intereference in this patient was demonstrated only in the measurement of fT4 and not in other analytes suggests that the interefernce was likely from endogenous antibodies, as heterphile antibodies often cause interference in the measurement of numerous analytes. These interferences can have important clinical consequences and may result in unnecessary investigations and inappropriate treatment with potentially unfavorable outcomes [17].

Interference in immunoassays from endogenous antibodies is still an unresolved and underestimated analytical problem that can have important clinical consequences. There is no single method that can rule out all interferences. It is important to recognize the possibility of such interferences and to implement protocols to identify these whenever possible in a timely fashion to prevent untoward consequences. As more and more biolgics or monoclonal antibodies are being used in clinical practice, such assay interferences may increase and vigilance is required in the recognition of such discordant results by both the clinician and the laboratory personnel.

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