Suspected hypogonadism and the importance of confirming the diagnosis - a case report

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ABSTRACT

Background: Hypogonadism is a common problem in middle-aged males and is often encountered in the primary care setting. Failure to accurately diagnose hypogonadism can lead to unintended consequences such as missing secondary causes or enabling anabolic steroid abuse.

Case Presentation: A 44-year-old male presented to the endocrinology clinic for further evaluation of abnormal testosterone levels. The patient had received a diagnosis of hypogonadism and was prescribed weekly testosterone injections, which he took for several weeks, but then discontinued therapy due to ineffective response. Serial laboratory evaluation revealed contradictory results and upon further investigation, an anabolic steroid screen returned positive for boldenone, an androgen used in veterinary medicine. After 4 months, his laboratories were repeated and showed a low total testosterone (TT) and free testosterone (free T), with luteinizing hormone (LH) and follicle stimulating hormone (FSH) inappropriately normal. Therapy was restarted using an FDA-approved formulation of testosterone and on subsequent follow-up, the patient had an improvement clinically and his repeat TT levels were normal, with free T slightly elevated.

Conclusion: There are two main takeaway points from this case that we would like to emphasize. First, a complete diagnostic evaluation of hypogonadism is vital to avoid missing potential secondary causes. Second, initiating testosterone replacement therapy (TRT) prematurely can obscure the diagnostic workup and potentially facilitate testosterone abuse.

Keywords: Case report, hypogonadism, hypothalamic-pituitary-gonadal (HPG) axis, accurate diagnosis, complete diagnostic pathway, testosterone replacement therapy, anabolic steroid abuse.

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Background

Hypogonadism is a common condition seen in clinical practice, with a prevalence of 38.7% in the primary care setting [1]. The symptoms of low testosterone include reduced libido, erectile dysfunction, anemia, hot flashes, depressed mood, fatigue, decrease in bone mass or muscle mass [2]. The cutoff criteria for testosterone levels in diagnosing hypogonadism remains controversial. The Endocrine Society guidelines suggest using the lower limit of normal total testosterone (TT) that has been calibrated to the Centers for Disease Control and Prevention (CDC) standard, which is 264 ng/dl and can be used for CDC-certified assays [3]. A complete evaluation of hypogonadism includes two things. The first is reproducible low morning TT level (lower limit cutoffs range between 230 and 350 ng/dl depending on reference and laboratory methodology used), followed by the measurement of follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels, to differentiate between primary and secondary hypogonadism [4]. We present a case of suspected hypogonadism in a patient who was started on testosterone replacement therapy (TRT) without a complete evaluation.

Subsequent laboratory evaluation revealed unexpected results that significantly affected our ability to make an accurate diagnosis.

Case Presentation

A 44-year-old male was referred to the endocrinology clinic by his primary care physician (PCP). The patient reported symptoms of fatigue, myalgia, reduced sexual drive, and erectile dysfunction. He was seen by an internet provider for these symptoms and had a solitary TT level checked, which came back low. He did not have any further laboratory testing such as LH or FSH, to differentiate between primary or secondary hypogonadism. He was prescribed 100 mg testosterone injections weekly. The patient discontinued the therapy after several weeks due to a lack of clinical improvement with some worsening of symptoms

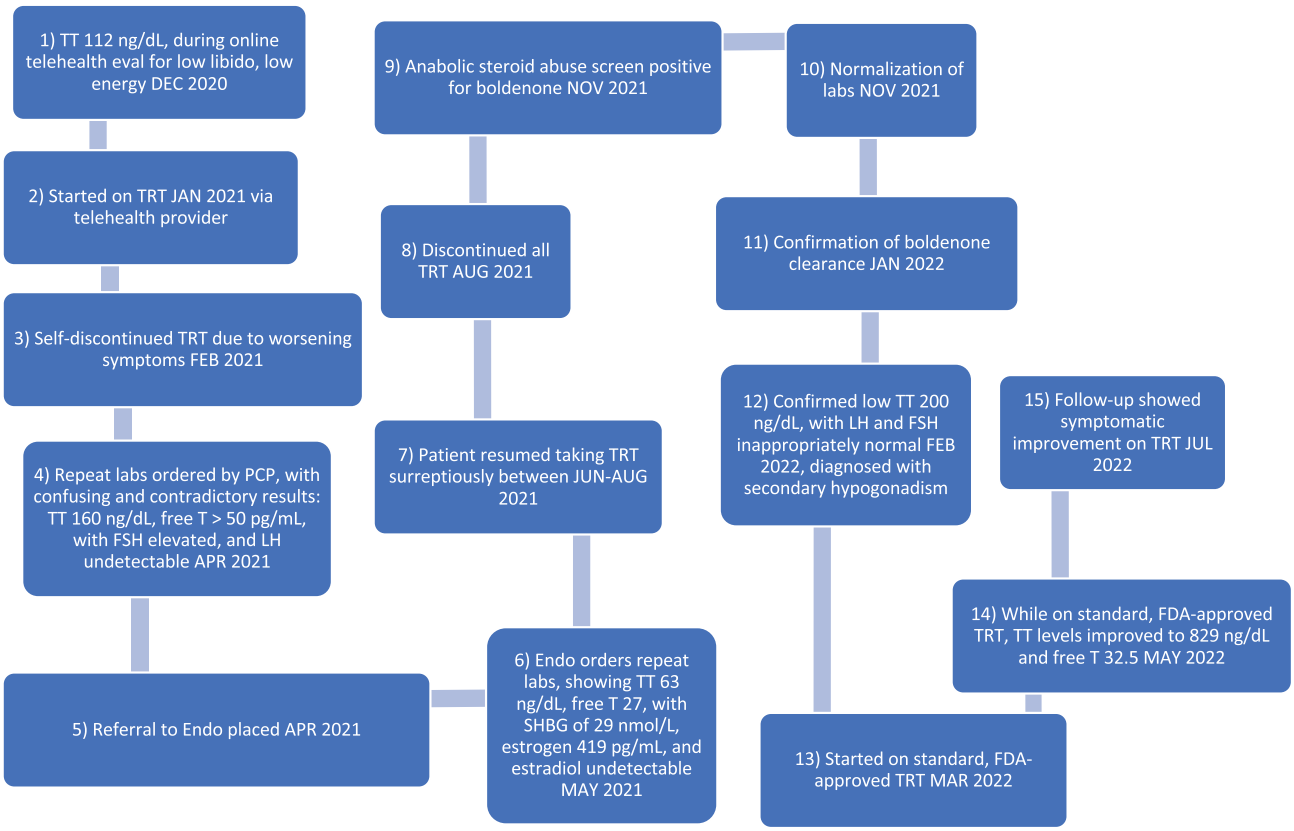

Figure 1. *Timeline.*

on the testosterone supplementation. Additional laboratory investigations returned: TT 160 ng/dl, free testosterone (free T) > 50 pg/ml, FSH 14.6 mIU/ml (1.55–9.74 mIU/ml), and LH < 0.22 mIU/ml (1.7-8.6 mIU/ml). He was referred to endocrinology for further evaluation. Physical examination revealed a well-developed, healthy-appearing male with average musculature. He had no cushingoid or acromegalic features. Extraocular muscle and visual field testing was normal. A breast examination revealed a normal appearance with no palpable gynecomastia. Genital examination revealed tanner V external genitals with a normal penis, and symmetric small testes, approximately 10 ml bilaterally. Skin examination showed no ecchymosis, striae, acanthosis, acne, or skin tags. Repeat laboratories showed TT 63.2 ng/dl and free T 27.4 pg/ml. Sex-hormone binding globulin level was also drawn and was within normal limits at 29.0 nmol/L (16.5-55.9 nmol/L). Hemoglobin was normal at 15.2 g/dl (12.6–16.8 g/dl), and the lipid panel showed a new marked low-density lipoprotein elevation of 185 mg/dl on direct LDL testing. The remainder of his lipid panel was normal, most notably his high-density lipoprotein was 45 mg/dl. His LDL 3 years earlier was calculated to be 116 mg/dl. He also had estrogen and estradiol levels checked which showed high estrogen at 419 pg/ml (56–213 pg/ml), undetectable estradiol < 5.0 pg/ml, undetectable estrone < 2.5 pg/ml, and undetectable estriol < 0.1 ng/ml. Upon further laboratory testing, a urinary anabolic steroid abuse screen came back positive for boldenone, an androgen often used in veterinary medicine. When the patient was questioned on whether he was taking any anabolic steroids, he firmly denied that he did so; however, he did admit to surreptitiously resuming his previously prescribed testosterone with the hope of feeling better despite his previous experience. On further inquiry, he reported that the testosterone came from a third-party compounding pharmacy used by his original androgen clinic. Upon discontinuation of the testosterone obtained from the compounding pharmacy, his laboratory numbers started to normalize, with TT 257 ng/dl and free T 20 pg/ml.

After approximately seven months off any TRT, testing confirmed that his boldenone levels had cleared. Two months later, further testing showed TT of 200 ng/dl and free T 20 pg/dl, with estrogen levels still elevated at 442 pg/ml and estradiol levels still undetectable at <5.0 pg/ml. With LH and FSH inappropriately normal at 2.7ml and 3.7 mIU/ml, the patient was diagnosed with secondary hypogonadism and was offered TRT using a standard, FDA-approved, formulation of 2% testosterone gel applied once daily. At follow-up after four months of TRT, he reported a significant improvement in his symptoms (fatigue, myalgias, reduced sexual drive, and erectile dysfunction) with no significant side effects or adverse events and had a repeat laboratory evaluation that showed normalization of his TT at 829.1 ng/dl and free T levels slightly elevated at 32.5 pg/ml. Refer to Figure 1 for a

concise summary of the timeline from initial presentation to symptomatic improvement. His high estrogen was evaluated with scrotal ultrasound and adrenal imaging to rule out hypersecretory tumors, and the cause of this finding was never identified. A mammogram confirmed gynecomastia. His estradiol level eventually normalized on TRT and his bone density was normal; however, his estrogen levels remained elevated.

Discussion

The worsening of the patient's symptoms, when he was started on TRT, could have been related to non-physiologic doses of boldenone, an anabolic-androgenic steroid (AAS), and dehydrogenated analog of testosterone, in the supplement. Our patient denied ever intentionally using boldenone, and we feel it is possible that the testosterone the patient obtained from the compounding pharmacy was either contaminated with boldenone or deliberately used as a compounding ingredient without the patient's knowledge. Regarding his confusing and contradictory laboratory results (low TT, high free T, high FSH, undetectable LH), the question of what effect boldenone had on these laboratory tests remains unanswered. Our opinion is that the resolution of his free T, FSH, and LH abnormalities at a time when he was confirmed to not be taking boldenone strongly suggests that these paradoxical laboratory abnormalities were directly related to the boldenone use. We believe his undetectable estradiol was related to the underlying hypogonadism and this was resolved with TRT using an FDA-approved agent. His elevated estrogen level appears to have been a red herring unrelated to hypogonadism, boldenone use, or any other underlying pathology.

As stated previously, after confirming low TT levels the next branch point in the diagnostic algorithm is obtaining FSH and LH levels, which is helpful to distinguish between primary and secondary hypogonadism [4]. If FSH and LH levels are low or inappropriately normal, then a diagnosis of secondary hypogonadism can be made. If FSH and LH levels are high, then primary hypogonadism is confirmed [4]. For our patient, one of the confusing findings at the beginning of his evaluation was a high FSH and undetectable LH. In our opinion, this raises the question of whether boldenone led to these contradictory laboratory results. In normal human physiology, higher levels of sex steroids exert negative feedback on the hypothalamic-pituitary-gonadal (HPG) axis and cause a decrease in both LH and FSH [5–6]. It is possible that the feedback on the human HPG axis occurs differently with boldenone than it does with human sex steroids. In a study published in *Toxicology and Industrial Health*, adult rabbits were injected with boldenone, resulting in both high FSH and high LH levels [7]. However, the specific effect of boldenone on human HPG axis physiology has not been studied. Another possible explanation for high FSH and low LH levels is an FSH-secreting pituitary adenoma [8]. This was considered during the patient's evaluation and a brain MRI was obtained, which was negative. Eventually, the return of the patient's FSH and LH to within normal limits after discontinuing the third-party testosterone lends support to the theory that the presence of boldenone either influenced or produced contradictory laboratory results.

Conclusion

We present a case that demonstrates the importance of a complete evaluation for hypogonadism before starting TRT. As demonstrated by this case, a high index of suspicion for AAS abuse is required as the drug history is often elusive and the presentation can be highly variable depending on the type and number of androgenic compounds, as well as the variable dosing regimens that can be used. Furthermore, the use of a compounding pharmacy raises the question of whether the boldenone was added without full disclosure to the patient. On a public health level, this has implications for licensure and regulation of these practices. On a provider level, this illustrates the importance of a non-judgmental approach to the patient suspected of AAS abuse and the possibility of using various androgenic compounds unknowingly. The lack of a complete diagnostic evaluation early on potentially enabled anabolic steroid abuse in our patient, and could also have resulted in missing potential secondary causes. After nearly a year-long evaluation, the patient was ultimately diagnosed with secondary hypogonadism by the endocrinology team. This enabled initiation of TRT using an FDA-approved regimen, in accordance with clinical practice guidelines from the Endocrine Society, with a good response to therapy. This case highlights the AAS-induced HPG axis dysfunction and presents a novel phenotype for AAS use. Challenges remain due to patient non-disclosure of medically relevant information and underscores the need for wider availability of AAS and metabolite testing in commercial laboratories. Finally, we find this case instructive for providers because the confirmation of the patient's diagnosis and treatment were ironically delayed by his initially incomplete diagnostic evaluation.

What is new?

This report serves to underscore already established diagnostic guidelines for hypogonadism and it emphasizes the importance of following the guidelines. A novel aspect of this manuscript is the positive boldenone result and the possible effects on the human HPG axis.

Disclaimer

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

Acknowledgment
None.

List of Abbreviations
CDC Centers for Disease Control and Prevention
FDA Food and Drug Administration
FSH Follicle stimulating hormone
LH Luteinizing hormone
MRI Magnetic resonance imaging
T Testosterone

Conflict of interest
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The patient approved the publication of this case report, with any identifiable information removed.

Ethical approval
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Summary of the case

1	**Patient (gender, age)**	44 y/o male
2	**Final diagnosis**	Secondary hypogonadism
3	**Symptoms**	Fatigue, myalgias, reduced sexual drive, and erectile dysfunction
4	**Medications**	100 mg testosterone injections weekly; 2% testosterone gel daily
5	**Clinical procedure**	N/A
6	**Specialty**	Internal medicine, family medicine, endocrinology