CASE REPORT

Unexpected cause of fever in a patient with untreated HIV

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SUMMARY

We report a case of a 27-year-old man with a history of untreated HIV who presented with fever, rash and leg cramps. Initial suspicion was high for an infectious process; however, after an exhaustive evaluation, thyrotoxicosis was revealed as the aetiology of his symptoms. Recent intravenous contrast administration complicated his workup to determine the exact cause of hyperthyroidism. Differentiation between spontaneously resolving thyroiditis and autonomous hyperfunction was paramount in the setting of existing neutropenia and the need for judicious use of antithyroid therapy. The inability to enlist a nuclear scan in the setting of recent iodinated contrast administration prompted alternative testing, including thyroid antibodies and thyroid ultrasound. In this case, we will discuss the diagnostic challenges of thyrotoxicosis in a complex patient, the sequelae of iodine contrast administration, effects of iodine on the thyroid and the predictive value of other available tests.

BACKGROUND

When thyrotoxicosis presents with fever, particularly, in an immunocompromised patient, diagnosis can be delayed while infectious aetiologies are pursued. Often, initial hospital testing includes imaging with iodinated contrast, which complicates subsequent thyroid evaluation. Thyrotoxicosis can be self-limited as a result of a destructive process such as viral thyroiditis and can also be persistent due to autonomous thyroid function, as seen in Graves' disease (GD) or toxic multinodular goitre. A timely and accurate diagnosis is necessary to minimise the adverse effects of untreated hyperthyroidism, such as arrhythmias, high output heart failure and thyroid storm. In a nuclear thyroid scan, uptake is increased in autonomous hyperfunction and low in the acute phase of destructive thyroiditis. However, thyroid uptake may also be reduced following the administration of an iodine load, and thus the contrast administered to our patient earlier in his admission precluded this option. Other available techniques to distinguish between aetiologies include the patient history, physical examination, thyroid antibody testing and thyroid ultrasound. The confirmation of the diagnosis prior to beginning therapy is necessary, as the use of antithyroid medications is not without risk. Although uncommon, drug-induced neutropenia is a dreaded and sometimes fatal complication of therapy.

CASE PRESENTATION

A 27-year-old man with a pertinent medical history of untreated HIV, untreated hepatitis C (HCV) and polysubstance use, presented to our emergency room with fever, chills, myalgia, fatigue, bilateral leg cramps with numbness in the thighs and a violaceous, pruritic, macular rash over his lower extremities. He denied neck stiffness, chest pain, dyspnoea or gastrointestinal distress. The patient had been diagnosed with HIV and HCV 1.5 years earlier and was started on antiretroviral therapy; however, he was compliant for only 2 days before stopping due to side effects of nausea and dizziness. At that time, his CD4 count was 340/ μ L and his viral loads for HIV and HCV were 22 476 copies per mL and 474 890 IU/mL, respectively. The patient then relocated to Arkansas, where he reported frequent camping trips, the most recent which was a few weeks prior to this current hospitalisation. During his most recent camping trip, he reported being bitten by ticks, which he identified as the Lone Star variety from a photographic tick line-up. Given several weeks of increasing fatigue and fevers, he decided to return to Pennsylvania to continue his care at our Institution. During the 15 hours bus ride, he reported a questionable syncopal event and awoke with headache and severe muscle cramps. He thus presented to our emergency room shortly after arriving back in Pittsburgh.

On admission, he was febrile at 101°F (38.3°C) with rigours and tachycardia. He showed decreased strength and sensation in his lower extremities, which were also diffusely tender, warm to the touch and hyperreflexive. His thyroid gland was not enlarged and had no nodules or carotid bruits. He had no proptosis or onycholysis. He did, however, display a macular and violaceous rash on his calves and shins bilaterally.

INVESTIGATIONS

Labs on admission showed white cell count 4.08 (4.40–11.30 10^9 /L), platelets 59 (145–445 10^9 /L) and absolute neutrophil count 1.47 (2–9.30 10^9 /L). An initial CT of the head without contrast was negative for any acute process. An MRI of the lumbar spine was performed to rule out spinal abscess and was unrevealing. A brain MRI, also without contrast (as the patient had reported a gadolinium allergy) was normal, and subsequently a CT of the head with contrast was done for a high suspicion of an intracranial infection. This was also normal. An extensive infectious evaluation was

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undertaken, along with biopsy of the skin lesions and lumbar puncture. With the exception of elevated C-reactive protein (CRP) and cryoglobulins, all other testing was negative. Skin biopsy revealed marked dermal red blood cell extravasation with mild perivascular and periadnexal lymphocytic infiltration. A repeat CD4 count and HIV viral load became available at this time and were 349/ μ L and 64 941 copies per mL, respectively. The patient was empirically maintained on doxycycline throughout this period.

Approximately 48 hours after the doxycycline and the CT of the head with contrast were administered, the patient felt a marked improvement in all of his symptoms. Thyroid function tests were subsequently ordered, revealing the findings of thyrotoxicosis as below:

Thyroid stimulating hormone (TSH): 0.052 (0.40–4.0 mcU/mL).

Free thyroxine (T4): 4.04 (0.70–1.90 ng/dL).

Free triiodothyronine (T3): 10.40 (1.76–3.78 pg/mL).

Total T3: 320 (80–200 ng/dL).

Antimicrosomal antibody (thyroid peroxidase antibody (TPOAb)): 125 (<40 IU/mL).

Thyroid-stimulating immunoglobulin (TSI): 41% (0–139%).

TSH receptor antibody (TRAb): 23.36 (<1.75 IU/L).

Thyroid ultrasound with colour Doppler revealed a mildly enlarged thyroid gland with a homogeneous background echotexture and normal flow.

DIFFERENTIAL DIAGNOSIS

The initial concern was for an infectious aetiology given the history of untreated HIV, fever and rash. Ehrlichiosis fit his exposures, symptoms and laboratory findings. Once thyrotoxicosis was identified, the differential diagnosis included the hyperthyroid phase of acute viral thyroiditis, autonomous hyperfunction (thyroid nodule or Graves' disease), and given the improvement in clinical picture after iodine load, the Wolff-Chaikoff effect. The time course was inconsistent with post-contrast iodine-induced thyrotoxicosis.

TREATMENT

The patient was empirically treated with broad-spectrum antibiotics, which was narrowed to doxycycline once the infectious workup was unrevealing. Doxycycline, however, was continued on high suspicion of tick-borne illness to complete a total of 14 days. The patient was started on antiretroviral therapy prior to discharge as well. Because the patient was clinically stable, the diagnosis of GD was not clear-cut, and there were concerns about antithyroid therapy in a patient with baseline neutropenia, the decision was made to hold methimazole until follow-up thyroid function tests could be obtained.

OUTCOME AND FOLLOW-UP

The patient continued to do well with improvement of his symptoms. He tolerated and remains on antiretroviral therapy. Labs

Table 2 Disparate results of thyroid testing

	Favoured	
	Graves' disease	Thyroiditis
Thyroid stimulating hormone receptor antibody	✓	✗
Ultrasound	✗	✓
Neutropenia	✓	✗
Examination	✗	✓
Thyroxine/triiodothyronine ratio	✗	✗
Thyroid peroxidase antibody	✓	✓
Improvement without thionamides	✗	✓

as outpatient are shown in [table 1](#). The findings from different tests in this patient favouring either GD or thyroiditis are also compared in [table 2](#).

DISCUSSION

Febrile illness in a patient with HIV should prompt a workup for infectious aetiologies; one study found that 79% of HIV-positive patients presenting with fever had an underlying infection.¹ The history of tick exposure expanded the possible underlying causes of fever, and Ehrlichiosis seemed probable given the patient's identification of a specific tick, his symptoms and haematological abnormalities. While the presentation of cutaneous Kaposi's sarcoma (KS) is variable, the violaceous character and location of the rash was consistent with the presentation of the early cutaneous form.² The development of KS highly correlates with CD4 counts, with rate ratios of 4.1, 3.6 and 18.9 for CD4 count ranges of 350–499, 200–349 and <200, respectively, when compared with CD4 counts of >500.³ Because the patient's CD4 count was unknown at presentation, the possibility of KS implied a high degree of immune compromise.

Such a high clinical suspicion for any diagnosis can leave clinicians susceptible to anchoring biases. As a result, a TSH was not checked until later in his hospital course.

Fever, however, is also common in hyperthyroidism. It is more likely that a fever is due to hyperthyroidism when it is accompanied by other manifestations of thyroid overactivity, such as diarrhoea, weight loss, tachycardia and agitation. Most patients with thyrotoxicosis from autonomous hyperfunction have an abnormal thyroid examination with diffuse goitre in the setting of GD or toxic nodular goitre. Our patient is remarkable in the paucity of other symptoms or findings to suggest underlying GD or toxic nodular goitre; he had no proptosis, goitre, nodule or onycholysis.

Determination of whether hyperthyroidism is due to a destructive process such as thyroiditis is usually approached by obtaining a nuclear thyroid scan. The expected finding during the hyperthyroid phase is a very low uptake of radionuclide. Although it is the gold standard test, it cannot be completed

Table 1 Results of thyroid function test during hospitalisation and follow-up

	Hospital admission	1 week	3 weeks	3 months	Normal reference range
Thyroid stimulating hormone	0.052	0.039	0.271	0.469	0.40–4.0 mcU/mL
Free thyroxine (T4)	4.04	2.57	1.09	1.03	0.70–1.90 ng/dL
Free triiodothyronine (T3)	10.40	–	–	3.80	1.76–3.78 pg/mL
Total T4	–	–	15.1	9.2	4.5–12 mcg/dL
Total T3	320	316	272	195	80–200 ng/dL

following an iodine load. Many patients get iodinated contrast administration during the course of an acute hospital stay, so this is not an infrequently encountered situation. It is important to recognise that there are alternative approaches to determine the aetiology of hyperthyroidism. These include the T3/T4 ratio, thyroid antibody testing and ultrasound. In our patient, it was difficult to come to a conclusion given the disparate results of our findings.

An autonomously overactive gland is expected to produce more T3 than T4, thus elevating the total T3/T4 ratio to >20. In our patient, only free T4 and free T3 levels were available and the ratio was found to be 2.57. A free T3/T4 ratio >4.4 (10^{-2} pg/ng) suggests that patient may have GD, and a low ratio of <2.2 suggests the possibility of subacute thyroiditis. An inconclusive ratio, between 2.2 and 4.4, requires further diagnostic testing.⁴

Another helpful diagnostic test is the TRAb assay. Our patient was TRAb positive. TRAb positivity, in the setting of hyperthyroidism is highly predictive of underlying GD with 95.5% of these patients being TRAb positive.^{5,6} Many clinicians in Europe, advocate the use of TRAb as a cost-effective primary test in the initial workup of hyperthyroidism, as it is useful in distinguishing GD from subacute painless thyroiditis.⁷ Our patient had the high M22-TRAb assay done in our hospital laboratory, which has been shown to have similar and excellent performance in diagnosing patients with GD as compared with the Mc4-TSAB assay.⁸ Functionally, TRAb may be divided into stimulatory antibodies that stimulate the thyroid (TSAb) and inhibitory antibodies that block the action of TSH (TBAb) and neutral antibody. Because of improvements in the accuracy of TSHR antibody (TRAb) testing, a positive TRAb result by a third generation assay in a thyrotoxic patient is considered by some to be diagnostic of GD.⁷ However, in one study,⁹ TSH binding-inhibiting immunoglobulin was detected in 8 of 53 patients (15.1%) with silent thyroiditis, and TSAb was detected in 10 of the 53 (18.9%) during the thyrotoxic phase. More recent evidence also demonstrates that TRAb may be present in patients with transient thyrotoxicosis.^{10,11} Thus, for clinically stable patients presenting without pathognomonic evidence of GD and elevated TRAb results, the possibility of self-limited thyroiditis should be considered.

Our patient was also TPOAb positive. TPOAb are present in the serum of 90%–95% of patients with autoimmune thyroiditis and are typically associated with Hashimoto's hypothyroidism. However, approximately 80% of patients with GD and 10%–15% of patients with non-autoimmune thyroid disease are TPOAb positive.¹² Additionally, serum antithyroid peroxidase concentrations are high in approximately 50% of patients with painless sporadic thyroiditis at the time of diagnosis, but elevations are not to the extent found in Hashimoto's thyroiditis.¹³

Another test that can support a diagnosis of thyrotoxicosis is thyroid ultrasound. In GD, ultrasound usually shows an enlarged, hypoechoic gland; however, the hypoechoic pattern is non-specific. It can also be seen in Hashimoto's and other types of thyroiditis. A more reliable evaluation for GD is with Doppler flow ultrasonography, which allows visualisation of increased blood flow velocity and intrathyroidal vascularity.¹⁴ Uchida *et al* used mean superior thyroid artery blood velocity and concluded it was highest in untreated GD followed by treated GD and then destructive thyroiditis.¹⁵ Colour Doppler can be considered a supplemental technique that might overtake radioactive iodine uptake test if further technical improvement and standardisation can be achieved.¹⁶ Our patient did not have characteristic findings of GD on thyroid colour Doppler ultrasound.

Treatment decisions were difficult since we had discordant results of testing, making it necessary to use clinical judgement

to determine whether the underlying disease process was GD or spontaneous silent thyroiditis. Our final decision to hold anti-thyroid therapy was based on risk–benefit analysis. Given the lack of clinical decompensation due to hyperthyroidism and the concern of using antithyroid medication in a patient with a baseline low neutrophil count, we chose to follow closely without therapy. The clinical course, with gradual spontaneous return to normal thyroid function over several weeks is consistent with a self-limited process.

In summary, the differential diagnosis of self-limited thyroiditis versus GD was difficult based on discordant test results and was confirmed only by the clinical course of resolution without antithyroid drug therapy. The findings of strongly positive anti-microsomal antibody (TPOAb) and paucity of other findings to suggest GD, as well as the evidence that TRAb can be positive in patients with subacute thyroiditis, supported our diagnosis of painless sporadic thyroiditis. Nonetheless, the positive TRAb and TPOAb put him at future risk of autoimmune disease. Close follow-up of this patient is planned.

Learning points

- In patients with complex presentations that include fever, consider hyperthyroidism early in the evaluation, as the administration of iodinated contrast may hinder the subsequent diagnosis. Taking time to entertain unanticipated alternate aetiologies may help mitigate anchoring biases.
- A clear understanding of the various thyroid tests (function, antibody and imaging) and the impact of time and other treatments are paramount, as confirming the aetiology of hyperthyroidism may inform a decision not to treat, that can be as impactful as a decision to start treatment.
- Particularly when nuclear thyroid scanning cannot be enlisted, there is an important role for checking thyroid stimulating hormone receptor antibody. This test is not frequently utilised in the USA and may have a niche in the setting of a recent iodine load.

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