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CASE REPORT

Primary hypothyroidism in a patient with germ cell tumor: A case report

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Abstract

Germ cell tumors (GCTs) are known to present with thyroid dysfunction, typically manifesting as hyperthyroidism due to human chorionic gonadotropin secretion. However, hypothyroidism among GCT patients is a relatively underexplored phenomenon, which could be attributable to low clinical suspicion and the potential masking of hypothyroidism by cancer-related symptoms. Moreover, the impact of hypothyroidism on cancer-related outcomes remains uncertain. Here, we present a case of incidentally detected primary hypothyroidism in a 16-year-old girl with an ovarian GCT. Remarkably, her condition improved at an unexpected rate after cancer-directed treatment. In our evaluation, we identified various causes of reversible hypothyroidism, all of which are comprehensively reviewed in this case report.

Keywords: Germ cell tumors; Primary hypothyroidism; Transient hypothyroidism; Rifampicin-induced thyroid dysfunction

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1. Background

Thyroid dysfunction among cancer patients remains relatively underexplored. Hypothyroidism in cancer is typically discussed in specific scenarios, such as following thyroid surgery/thyroid ablation, post-radiation therapy, targeted therapy, or immunotherapy.[1] However, outside of this context, clinical suspicion for primary hypothyroidism may be low. This lack of clinical suspicion is compounded by the fact that hypothyroidism symptoms are often non-specific and can easily be attributed to the malignancy itself.[1] The potential consequences of inadequately managing hypothyroidism on cancer-related outcomes are significant but largely unknown. This issue is particularly pertinent in pediatric oncology, where advancements in care and knowledge have led to improved outcomes compared to adult cancer patients. Moreover, untreated hypothyroidism in this age group can impair pubertal growth. This information holds particular relevance among curable malignancies like germ cell tumors (GCT). Here, we present a case of incidentally detected hypothyroidism in a patient with an ovarian GCT. Furthermore, we review possible causes of reversible hypothyroidism, which may carry significance among cancer patients.

2. Case presentation

A 16-year-old girl presented to the emergency department with a 3-month history of progressive abdominal distension and shortness of breath. Subsequent detailed

clinical evaluation and pathological assessment of an omental biopsy confirmed Stage IV ovarian GCT (dysgerminoma). The level of the tumor biomarker (serum lactate dehydrogenase [LDH]) over the treatment course is depicted in Figure 1. Before presenting at our institute, the patient received a 2-month treatment of antitubercular therapy elsewhere, receiving daily rifampicin, isoniazid, ethambutol, and pyrazinamide under the presumption of abdominal tuberculosis. However, despite this treatment, there was no microbiological evidence of tuberculosis, and the patient experienced no clinical improvement. After discussion on a multidisciplinary tumor board, neoadjuvant chemotherapy comprising etoposide and cisplatin was initiated, taking into account her poor performance score and extensive disease burden.

Bleomycin was omitted from the therapy regimen due to the patient's poor lung condition. Subsequently, the patient underwent four cycles of chemotherapy administered at 21-day intervals (cumulative doses: etoposide = 2600 mg and cisplatin = 520 mg). Following the treatment, there was a significant improvement in the patient's health status. The next steps involved radiological response assessment and surgical intervention. However, due to a nationwide lockdown imposed during the COVID-19 pandemic, the patient's treatment plan was delayed by 1 month. Meanwhile, the patient developed recurrent abdominal distension accompanied by ascites, pleural effusion, and an elevation in serum LDH levels (Figure 1). Despite these developments, the patient proceeded with the initial plan, undergoing pre-anesthetic evaluation and a contrast-enhanced computer tomography (CECT) scan with iodinated contrast to assess disease status. Notably, during the evaluation, serum thyroid-stimulating hormone (TSH) levels were found to be elevated (Figure 2). However, symptoms of hypothyroidism, such as growth failure, constipation, and lethargy, were absent, nor was there any history of thyrotoxic episodes, neck pain, or neck swelling.

The patient's pubertal status was post-menarcheal. However, following the initiation of chemotherapy, she developed amenorrhea. Despite this, she maintained appropriate stature for her age, with a Tanner staging of B5P5, and no goiter was observed upon neck examination. The neck ultrasonography detected no abnormality. Confirmation of hypothyroid status was confirmed through serum TSH, free triiodothyronine (FT3), and free tetraiodothyronine (FT4), as depicted in Figures 2-4. Notably, the antithyroperoxidase antibody (ATPO) level was elevated at 269 U/L (normal range <60 U/L). The clinical impression suggested an incidentally detected subclinical hypothyroidism due to Hashimoto's thyroiditis. Following an increase in TSH levels noted after CECT, the

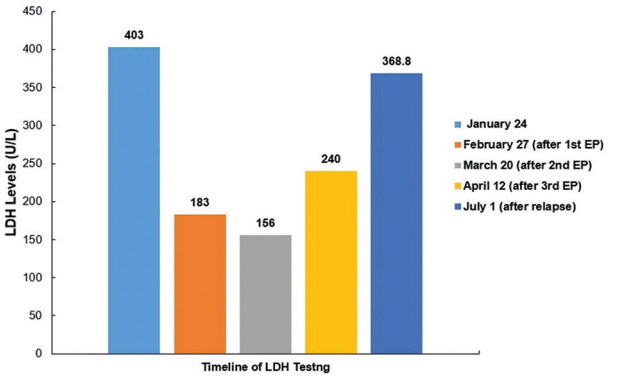

Figure 1. Serum lactate dehydrogenase (normal range value: 0 – 247 U/L) response after starting first-line chemotherapy (etoposide and cisplatin) treatment and after the first relapse

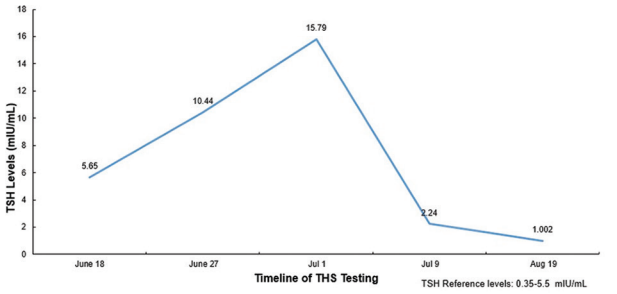

Figure 2. Trends of serum thyroid-stimulating hormone levels during treatment course

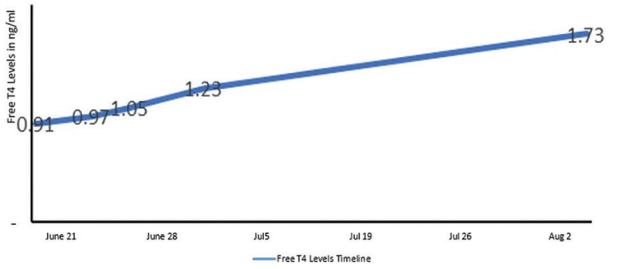

Figure 3. Trends of serum-free T4 levels (NV): 0.87 – 1.7 ng/mL Abbreviation: NV: Normal range value.

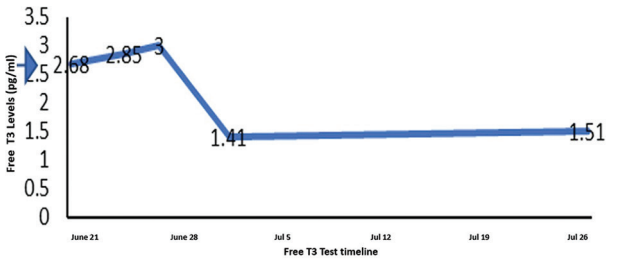

Figure 4. Trends of serum-free T3 levels (NV): 2.3 – 4.2 ng/mL Abbreviation: NV: Normal range value.

Table 1. The different etiologies reported for transient hypothyroidism with the recovery of thyroid function tests either spontaneously or after treatment

Type of hypothyroidism	Etiology of transient hypothyroidism	Clinical presentation	Thyroid function tests and antithyroid antibodies (ATPO or ATG)	Treatment and outcome
Iodinated contrast media (ICM)-related hypothyroidism[4]	The thyroid gland fails to escape from the acute Wolff-Chaikoff effect	1. Euthyroid patients with underlying conditions. Risk factors: • Hashimoto's thyroiditis. • Euthyroid Graves' disease was previously treated with surgery/radioactive iodine/ antithyroid drug therapy. • History of partial thyroidectomy. • History of post-partum lymphocytic thyroiditis or subacute thyroiditis. • History of interferon- therapy. • History of type 2 amiodarone-induced thyrotoxicosis. • Fetus or neonates.	1. The duration between the exposure and incident hypothyroidism varied between 50 and 294 days. The presence of TPO antibodies, a marker of thyroid autoimmunity, may indicate a pre-disposition to iodine-induced thyroid dysfunction.	1. If the serum TSH is >10 mIU/L, treatment with levothyroxine is warranted. 2. When the serum TSH is 5 – 10 mIU/L, treatment can be considered symptomatic. 3. Serum TSH should be measured every 6 – 12 weeks. 4. Some patients with transient iodine-induced hypothyroidism later develop permanent hypothyroidism. 5. There is no indication of routine universal screening after ICM. 6. Monitoring is required in case with co-existing thyroid disorders.
Subacute thyroiditis[5]	1. Viral infection (genetically Pre-disposition). 2. Destructive autoimmunethyroiditis.	1. Neck pain: Cardinal symptoms (sudden/gradual). 2. Dysphagia. 3. Tender/enlarged thyroid gland. 4. Systemic symptoms: fever, fatigue, arthralgia/myalgia, and/or anorexia. 5. Thyroid dysfunction has atriphasic course. Hyperthyroid phase: 60% of patientsand peak after 7 days of symptoms. Hypothyroid phase: 30 – 60% of patient. Euthyroid phase: Recovery of symptoms and thyroid function test.	1. Depend on the phase of the diseased one. The T3 – T4 ratio is often relatively low. Thyroid antibodies: usually absent. Positive antibodies: (Hypothyroid phase). Antibodies disappeared: (The recovery phase).	1. The entire clinical course typically lasts about 3 months. 2. Levothyroxine is rarely needed in the early hypothyroid phase. 3. Recurrence rate: 1.4 – 4% 4. Late-onset hypothyroidism orhyperthyroidism: Is reported without specific frequencies.
Rifampicin-related thyroid dysfunction	Hypothyroid patients[6] (retrospective analysis).	1. The patient suffered from TB (active/ latent/NTM) infection and was on levothyroxine therapy for (N=71). Suppression (PTC) replacement for hypothyroidism.	1. After rifampicin (median 32 weeks): 2. TSH levels increase (P<0.001). 3. FT4 levels decrease (P<0.001). 4. Increased need for LT4 dose. 5. TSH-suppression group: 50% (23/46). 6. Replacement group: 24% (6/25).	NA.
	Euthyroid patient[7] (case report)	1. Among 67 pulmonary tuberculosis patients: antithyroid antibodies (ATPO and ATG); negative: 42 and positive: 25.	1. 3/67 patients exhibit an elevation in TSH levels after 28 days of treatment with rifampicin and required LT4 replacement therapy.	

(Cont'd...)

Table 1. ***(Continued)***

Type of hypothyroidism	Etiology of transient hypothyroidism	Clinical presentation	Thyroid function tests and antithyroid antibodies (ATPO or ATG)	Treatment and outcome
			2. All three had raised ATPO antibodies at baseline. FT4 levels were reduced.	After discontinuation of rifampicin patient become euthyroid and LT4 replacement therapy was stopped.
Paraneoplastic hypothyroidism	Consumptive hypothyroidism:[8] Rare condition reported with vascular tumors mainly in infants	A severe form of hypothyroidism. 2. Infants: Median age at diagnosis of 1.6 months. 3. Conditions: Hepatic hemangioma and hepatic hemangioendothelioma. 4. Adults: Gastrointestinal stromal tumor, fibrous tumor, and hepatic hemangioma	1. TSH level (median of 64 mIU/L; P25 – P75: 26 – 82), low T_4 and T_3, and elevated levels of rT_3. 2. ATPO: NA	Thyroid hormone replacement requirement is significantly reduced after tumor resection

Abbreviations: ATG: Antithyroglobulin antibody; ATPO: Antithyroid peroxidase; FT3: Free triiodothyronine; FT4: Free tetraiodothyronine; NA: Not available information; NTM: Non-tubercular mycobacterium; TB: Tubercular mycobacterium; TSH: Thyroid-stimulating hormone; T3: Triiodothyronine; T4: Tetraiodothyronine; LT4: Levo-tetraiodothyronine; PTC: Papillary thyroid cancer.

endocrinology team recommended repeating the thyroid function test after 1 week. Subsequent follow-up revealed a further rise in TSH levels (Figure 2).

Meanwhile, the CECT scan report indicated a partial response in tumor size; however, ascites were identified as a new finding. Cytological analysis of ascitic fluid confirmed the presence of malignant cells, indicating cancer progression. Consequently, the treatment plan was revised to include salvage chemotherapy. The patient commenced thyroxine replacement therapy at a daily dose of 75 µg following an endocrinologist review. Concurrently, salvage chemotherapy consisting of carboplatin, paclitaxel, and ifosfamide (TIP regime) was initiated. The subsequent trends in free FT3, FT4, and TSH levels are presented in Figure 2-4. Tragically, following administration of the second dose of salvage chemotherapy, the patient succumbed to her illness due to severe febrile neutropenia.

3. Discussion

Literature is scarce on primary hypothyroidism among patients suffering from GCT. Following an extensive literature search of the PubMed and Scopus databases, only one case report documenting overt hypothyroidism in ovarian GCTs was identified.[2]

In our case, the initial suspicion for primary hypothyroidism was the incidental detection of Hashimoto's thyroiditis. However, the loss of thyroid function in Hashimoto's thyroiditis is irreversible and progressive. Typically, stabilization of TSH levels with levothyroxine replacement therapy requires 3 – 4 half-lives, necessitating reevaluation of TSH levels after 4 – 6 weeks.[3] However, in our patient, TSH values normalized (<5 IU/L) within 10 days of thyroxine replacement and remained within normal limits after 6 weeks (Figure 2). It indicates that the thyroid dysfunction was transient and reversible, either spontaneously or with the intervention of chemotherapy.

We conducted a review of the literature focusing on reversible causes of hypothyroidism that may be relevant in cancer patients, aiming to elucidate our case further. Iodinated contrast media (ICM), as described in Table 1 in relation to hypothyroidism, appears to be the most reasonable explanation in our case, especially considering the presence of risk factors and the temporal relationship. Despite evidence of autoimmune thyroiditis and the subsequent rise in TSH levels following a CECT scan, the observed rate of TSH recovery (Figure 2) exceeded that reported in existing literature.[4] While CECT scans are standard diagnostic tools in cancer patient management, the literature regarding their impact on thyroid function remains scarce. Identifying patients who require thyroxine replacement or those likely to recover spontaneously is challenging in cancer care. We opted to treat based on serum TSH levels after consulting pediatric endocrinologists. Subacute thyroiditis emerged as the next probable explanation, as shown in Table 1. However, the absence of cardinal signs and symptoms without a preceding hyperthyroid phase was against this possibility.

Nevertheless, these features could be silent[5] or masked under cancer-related symptoms. Drugs (other than iodine-containing) related to thyroid dysfunction are a challenge among patients on multiple medicines. In our patient's drug record, rifampicin was the only drug found to cause thyroid dysfunction or hypothyroidism.[6] However, the information is based on a few case reports, and the data is

not robust.[7] Moreover, there was no temporal relation to the event of hypothyroidism.

We acknowledge the potential limitations of our case report, including its retrospective nature and the absence of long-term follow-up data. Although the hypothyroidism was mild, it appears to have been unmasked solely by the tumor process. Since the patient was consulted and managed in coordination with our expert endocrinologist at our tertiary care academic institute, we cannot disregard this atypical clinical observation in ovarian GCT patients.

Consumptive hypothyroidism syndrome is a rare yet severe form of paraneoplastic hypothyroidism. Literature highlights the rapid rise in TSH, high demand for thyroxine, and faster normalization of thyroid function with cancer-directed treatment in various case reports (Table 1). Consumptive hypothyroidism syndrome was primarily reported among neonates and infants with vascular tumors involving the liver. Nevertheless, there are occasional case reports among patients with different histologies in other age groups.[8] To the best of our knowledge, in GCT, the condition was not reported. In the present case, we attribute the observed thyroid dysfunction to ICM-related hypothyroidism in the presence of risk factors and temporal relationships. However, a longer follow-up would have been more informative, which was unfortunately not possible. The case encourages us to think beyond the conventional understanding of thyroid dysfunction in cancer patients.

4. Conclusion

ICM and drugs represent critical factors that can predispose susceptible individuals to thyroid dysfunction. Given the frequent use of radiological imaging and polymedicine in cancer patients, the implications of such events require further elaboration. Notably, cancer-specific symptoms may mask the signs and symptoms of subacute thyroiditis. Moreover, the incidence of primary hypothyroidism among cancer patients, excluding specific conditions, is probably underreported. There is a pressing need to understand the impact of hypothyroidism on cancer-specific outcomes, particularly in treatable malignancies.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Parmod Kumar, Amit Sehrawat
Investigation: Parmod Kumar, Amit Sehrawat
Methodology: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Written consent was given by the patient to participate in this study.

Consent for publication

Written consent was given by the patient to publish her data in this study.

Availability of data

Anonymized case data are available upon request from the corresponding author for academic purposes only.

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