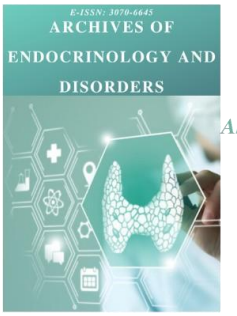

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Case Report

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Secondary Hemophagocytic Lymphohistiocytosis Associated with Follicular Thyroid Adenoma: A Case Report

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Abstract

Secondary Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome resulting from uncontrolled immune activation, most commonly triggered by infections, autoimmune diseases or hematological malignancies. Its association with solid tumors is uncommon and involvement of thyroid tumors is exceedingly rare. We report a case of a 49-year-old woman who presented with prolonged fever and systemic inflammatory features and was diagnosed with secondary HLH in association with follicular adenoma of the thyroid. The patient fulfilled the established diagnostic criteria for HLH, including cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and bone marrow hemophagocytosis. She responded to immunomodulatory therapy with corticosteroids and Intravenous Immunoglobulin (IVIG), followed by definitive surgical management of the thyroid tumor. Following thyroidectomy and appropriate adjuvant care, the patient achieved sustained remission of both HLH and thyroid tumor. This case highlights a rare but important association of HLH with follicular thyroid adenoma and underscores the need to consider solid tumors as potential triggers of secondary HLH.

Keywords: Hemophagocytic Lymphohistiocytosis (HLH); Hyperferritinemia; Thyroid Adenoma; Hyperinflammatory Syndrome

Introduction

Hemophagocytic lymphohistiocytosis is a severe hyperinflammatory condition characterized by pathological immune activation, leading to excessive cytokine release and multiorgan dysfunction. Secondary HLH is most frequently associated with infections particularly viral infections autoimmune disorders and hematological malignancies. Solid tumor-associated HLH is rare, with only sporadic reports involving carcinomas of the lung, breast, gastrointestinal tract and genitourinary system [1].

Thyroid neoplasms are not traditionally recognized as triggers for HLH. When HLH occurs in such settings, establishing causality is challenging due to frequent confounders such as infection, treatment-related immune modulation and critical illness. Reporting such cases is essential to broaden clinical awareness and improve early recognition and management of this highly fatal condition.

Case Presentation

A 49-year-old female presented with intermittent high-grade fever for two months, associated with constitutional symptoms. Clinical examination revealed an enlarged thyroid gland. Laboratory evaluation revealed primary hyperthyroidism for which she was started on antithyroid drugs including carbimazole and propranolol. Contrast-Enhanced Computed Tomography (CECT) of the neck and thorax demonstrated an enlarged thyroid gland (right lobe- 4.1 * 4.2 * 10.8 cm, left lobe- 5.3 * 3.9 * 10.3 cm) with calcifications and retrosternal extension, along with multiple enlarged cervical and mediastinal lymph nodes.

Whole-body ^18F-FDG positron Emission Tomography-Computed Tomography (PET-CT) revealed an enlarged thyroid gland containing multiple hypo-enhancing nodules with calcific foci, demonstrating increased metabolic activity. There was evidence of posterior tracheal compression and extension into the prevascular space. Fine-needle aspiration cytology was suggestive of a follicular neoplasm, oncocytic type (cat IV). Surgical oncology consultation recommended definitive surgical management following medical stabilization.

Despite antithyroid drugs, patient had persistent clinical presentation of fever, fatigue and intermittent breathlessness. Laboratory evaluation revealed anemia (Hb= 4.5 gm/dl) and thrombocytopenia (PLT= 28000/cu.mm), markedly elevated serum ferritin (47600 ng/mL), transaminitis (ALT = 233 IU/L, AST = 226 IU/L), hypertriglyceridemia (973 mg/dl) and hypofibrinogenemia (83 mg/dl). Bone marrow examination demonstrated hemophagocytosis. Based on HLH-2004 criteria, a diagnosis of HLH likely secondary to neoplastic etiology was established after ruling out infections and autoimmune disorders. The patient was initially treated with systemic corticosteroids, with inadequate clinical response. Intravenous immunoglobulin was subsequently administered at a cumulative dose of 2 g/kg, resulting in significant clinical and biochemical improvement, including recovery of platelet counts (340,000/cu.mm) and normalization of inflammatory markers - ferritin (129 ng/mL), fibrinogen (305 mg/dl) and triglycerides (170 mg/dl) (Table 1).

In view of the need for prolonged immunosuppression, viral screening was performed. The patient was positive for anti-HBc total antibodies, negative for HBsAg and had detectable hepatitis B virus DNA (1,100 IU/mL). Antiviral therapy with Entecavir 0.5 mg once daily was initiated.

Following medical optimization, the patient underwent total thyroidectomy with central neck dissection for definitive management, tissue sample was sent for histopathological examination which revealed follicular adenoma (4.2 cm), right lobe with nodular follicular disease in the background in both the lobes (Fig. 1,2). Postoperatively, calcium supplementation was initiated and levothyroxine replacement was started seven days after surgery. The postoperative course was uneventful, with no surgical complications or metabolic derangements.

She was discharged on dexamethasone as per HLH treatment protocol - 10 mg/m^2 for 2 weeks followed by tapering over eight weeks. On follow-up, the patient remained clinically stable, with no evidence of HLH recurrence.

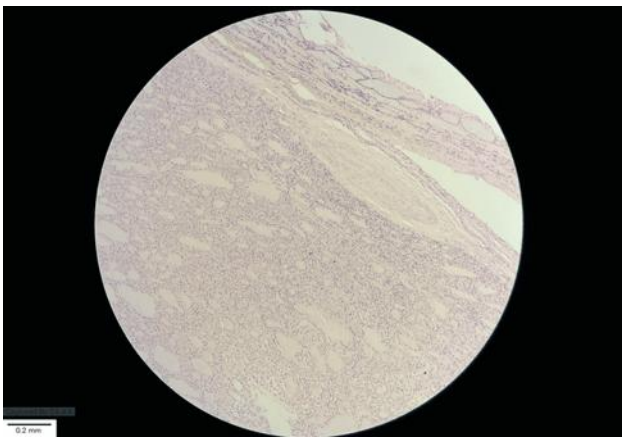

Figure 1: Histopathology of tumor tissue- Low power view (10x) showing encapsulated lesion and tumor, not infiltrating the capsule.

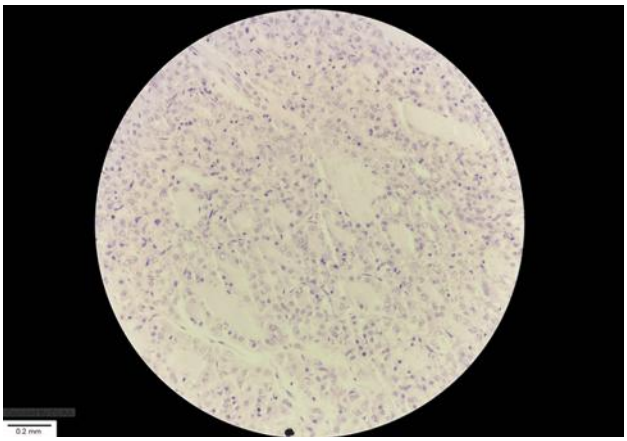

Figure 2: Histopathology of tumor tissue- High power view showing macro and micro-follicles.

Lab Marker	Day 01	Day 03	Day 05	Day 09	Day 12	Follow up 1	Follow up 2
Ferritin (ng/mL)	47600	30000	21500	11500	3350	2280	129
Fibrinogen (mg/dl)	83	103	117	121	144	171	305
Triglycerides (mg/dl)	973	864	486	322	250	190	170
ALT (IU/L)	233	109	67	54	36	32	25
AST (IU/L)	226	49	39	37	32	31	29

Table 1: Sequential ferritin, fibrinogen, triglyceride, ALT, AST levels, illustrating subsequent recovery after treatment during hospitalization and on follow up.

Discussion

Secondary HLH results from impaired cytotoxic function of natural killer cells and cytotoxic T lymphocytes, leading to persistent macrophage activation and excessive cytokine release. While malignancy-associated HLH is most commonly linked to lymphomas, particularly of T-cell and NK-cell origin, its association with solid tumors is increasingly recognized but remains rare.

The pathophysiological mechanisms underlying solid tumor-associated HLH are not fully understood. Proposed mechanisms include tumor-driven immune dysregulation, chronic antigenic stimulation, cytokine secretion by tumor cells and secondary immune activation due to tissue necrosis or infection. In the present case, although infection was initially present, HLH persisted despite resolution of pneumonia and sustained remission was achieved only after immunomodulatory therapy and definitive tumor resection, supporting a causal association with the underlying thyroid carcinoma.

In a large review of adult HLH, Ramos-Casals, et al., reported malignancy as a major trigger in adults but noted that over 90% of malignancy-associated HLH cases were linked to hematologic cancers, predominantly lymphomas [2]. Solid tumors were distinctly uncommon and thyroid neoplasms were not prominently represented, which makes this case exceptionally rare.

Wakefield, et al., reported that secondary HLH has been linked to several malignancies, but its association with papillary thyroid carcinoma is rare [3]. Although causality cannot be confirmed, a coincidental occurrence is unlikely. Given this association, patients with HLH should undergo thorough evaluation for underlying malignancy, including bone marrow examination and appropriate imaging studies.

Recommendations by La Rosée, et al., emphasized that solid tumor-associated HLH presents unique diagnostic and therapeutic challenges, particularly because systemic inflammation may mimic sepsis or advanced malignancy [4]. They highlighted the importance of early recognition and individualized immunosuppressive strategies, rather than uniform application of general HLH protocols.

Lee, et al., documented HLH secondary to autoimmune thyroiditis, wherein immune-mediated inflammation rather than neoplasia served as the trigger [5]. The patient responded favorably to corticosteroid monotherapy stating the concept that the underlying etiology of HLH strongly influences therapeutic response and outcome, which in our case was follicular neoplasm and showed resolution after thyroidectomy [4].

Follicular thyroid adenoma is typically considered an indolent neoplasm; however, this case suggests that even well-differentiated benign solid tumors can, in rare instances, trigger profound immune dysregulation. Recognition of this association is crucial, as early diagnosis and prompt initiation of HLH-directed therapy significantly improve outcomes.

Conclusion

This case illustrates that the occurrence of secondary hemophagocytic lymphohistiocytosis in association with thyroid follicular adenoma is unlikely to be a mere coincidence. Clinicians should maintain a high index of suspicion for HLH in patients with solid tumors who present with persistent fever, cytopenias and hyperinflammatory laboratory features [6]. Early diagnosis, timely immunomodulatory therapy and definitive treatment of the underlying malignancy are essential for favorable outcomes. Reporting such rare associations contributes to improved understanding of the diverse triggers of secondary HLH and may aid in earlier recognition in similar clinical scenarios.

Clinical and Therapeutic Implications

Consistent with the recommendations of La Rosée, et al., this case supports a stepwise, individualized approach to adult secondary HLH:

1. Early recognition in patients with unexplained fever, cytopenias and extreme hyperferritinemia
2. Prompt immunomodulation tailored to patient stability and comorbidities
3. Definitive treatment of the underlying trigger, when feasible

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not Applicable.

Authors' Contributions

All authors contributed equally to this paper.

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