Down syndrome with primary thyroid diffuse large B-cell lymphoma and Hashimoto thyroiditis

A CARE compliant case report

Luyang Wei, MMed¹, Ning Zhao, MD², Yalun Li, MMed¹, Xiaodan Zheng, MMed³, Huaxin Zhang, MMed⁴, Zhongtao Zhang, PhD⁴.

1. Introduction
Down syndrome (DS), the most common chromosomal disorder, is associated with several concomitant diseases, including thyroid disorders.-autoimmune thyroid disease (ATD), in particular Hashimoto thyroiditis (HT), is common in adults with DS. HT is a well-established risk factor for primary thyroid lymphoma (PTL), which is rare, comprising approximately 5% of all thyroid malignancies, and less than 3% of all extra-nodal lymphomas. The vast majority of PTLs are non-Hodgkin lymphomas derived from B-cells, including diffuse large B-cell lymphoma (DLBCL), mucosa-associated lymphoid tissue lymphoma (MALT), and mixed subtype (combination of DLBCL and MALT). The prognosis of DLBCL is worse than that of MALT.

Both DS and PTL are rare diseases, and concomitant primary thyroid DLBCL and HT in a patient with DS has not been reported before in the literature to our knowledge. Therefore, we present such a case here, which was associated with an adverse outcome (death), and discuss the clinical features, diagnosis, treatment, and prognosis.

Written informed consent was obtained from the patient's direct relative for publication of this case report and related images. Ethical approval was obtained from the Human Ethics Committee of Beijing Friendship Hospital, Capital Medical University.

2. Case Report
A 43-year-old woman with DS was referred to our hospital in January 2018, due to a 1 month history of an enlarging right-sided neck mass with associated dyspnea, neck ache, hoarseness, and dysphagia. Typical B symptoms (fever, night sweats, or weight...
loss) were not present. The patient’s medical history was notable for Hashimoto thyroiditis, subclinical hypothyroidism, and contracting influenza just prior to the onset of symptoms. Physical examination revealed the typical signs of DS, including short stature (148 cm), mental retardation, characteristic facies (oblique orbital fissures, small ears, and open mouth with protruding tongue and salivation), short broad hands with transverse palmar creases, and hypotonia. There was a large tender neck mass measuring 8 × 8 cm on the right side, which had shifted the trachea to the contralateral side.

After admission, laboratory testing revealed hyperuricemia, and serum hormone measurements showed a thyroid-stimulating hormone (TSH) level of 30.99 uIU/L (reference range, 0.49–4.91), free T4 level of 0.74 ng/dL (reference range, 0.59–1.25), free T3 value of 4.00 pg/mL (reference range, 2.14–4.21), thyroglobulin antibody level of 0 U/mL (reference range, 0–4.00), and thyroid peroxidase antibody level of 400 U/mL (reference range, 0–9.00). Thyroid ultrasonography (US) revealed a hypoechoic cystic-solid mass measuring 8.1 × 7.0 × 6.9 cm in the right lobe, with a slightly rough border and heterogeneous echotexture (Fig. 1A). Color Doppler ultrasound showed a small number of blood flow signals in the mass. Neck computed tomography (CT) scan revealed a large mass in the right lobe compressing the trachea, laryngopharynx, and oropharynx (Fig. 1B). Laryngoscopy showed obvious distention of the right hypopharyngeal sidewall. Abdominal US did not detect enlarged lymph nodes. Based on the imaging results, benign neoplasm or organized hematoma was suspected; malignancy was also considered. After multidisciplinary discussion, we did not prefer conservative treatment, and elected to perform a thyroidectomy with dissection of the central compartment because of the patient’s severe tracheal compression.

During the operation, we strongly suspected the possibility of malignancy because infiltrative growth of the mass into the surrounding tissues and considerable edema were observed. The mass was not clearly defined within the thyroid cartilage, cervical sheath, trachea, or the anterior cervical musculature. Large amounts of lymphoid cell and heterotypic cell nest infiltration were observed in the intraoperative frozen section biopsy, thus, it was considered malignant, favoring a lymphoma diagnosis. We then proceeded with palliative unilateral thyroidectomy. Histopathological analysis of the biopsy specimen revealed diffuse large lymphoid cells. In addition, the presence of eosinophilic change in lymphatic follicles contained within the capsule suggested Hashimoto thyroiditis (Fig. 2). Immunohistochemical
staining revealed large lymphoid cells diffusely immunoreactive to CD20, CD30, CD10, B-cell lymphoma (BCL) 6, and multiple myeloma oncogene (MUM) 1; immunoreactivity to BCL-2, cyclin D1, CD3, and CD5 was negative. The Ki-67 index was >80% (Fig. 3). A diagnosis of primary thyroid DLBCL with HT was confirmed. Staging evaluation did not reveal any other involvement (stage IE).

The patient was discharged home with a prescription of levothyroxine 50 mcg per day and we strongly recommended treatment with combination targeted therapy and chemotherapy (R-CHOP: the monoclonal antibody rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) after recovery from surgery. Unfortunately, she died 3 weeks after the operation due to asphyxia caused by uncontrollable growth of recurrent tumor.

3. Discussion

Yang et al reported a case of DS with MALT and cerebral infarction in 2000, but there has been no reported case of DS with coexisting primary thyroid DLBCL and HT, to our knowledge. The association between DS and thyroid disease is well known, with reported coexistence rates ranging 4% to 28%.[1,2,10,11]
Thyroid dysfunction is exceedingly common in adults with DS compared to that in children who have the syndrome. (12) Both hyper- and hypothyroidism occur frequently in patients with DS, however, hypothyroidism is more common; subclinical hypothyroidism, characterized by a normal free T4 level and elevated TSH level, occurs in 13.0% to 36.3%. (11–13) In this case report, subclinical hypothyroidism was present in our patient.

One of the most typical clinical features of DS patients is their susceptibility toward several autoimmune diseases, especially Hashimoto thyroiditis (HT). (13,14,15) Baxter et al. indicated in their study that the chromosomal abnormality impairs the normal mechanisms which protect against autoimmunity to the thyroid, and pre-existing autoantibody formation in the mother favors the development of a chromosomal abnormality in the child. (12) In addition, dysregulation of the immune system in DS patients, with consequent defect of inhibitory activity, is thought to be the cause of an increased prevalence of autoimmune thyroid diseases in this population. (16,17) Patients with DS also often have an earlier presentation of HT with a more severe biochemical and clinical evolution. (18)

Large epidemiological studies have shown that autoimmune disorders consistently increase the risk of developing lymphoma. This link appears to be stronger for some autoimmune diseases and certain non-Hodgkin lymphoma subtypes. (19) Regarding PTL, the majority are B-cell lymphomas, with DLBCL the most common, accounting for 50% to 70% of all cases of PTL; rare cases of Hodgkin and T-cell lymphoma have been reported as well. (7,20) PTL is staged based on the Ann Arbor staging criteria, and certain non-Hodgkin lymphoma subtypes. (19) Regarding PTL, the majority are B-cell lymphomas, with DLBCL the most common, accounting for 50% to 70% of all cases of PTL; rare cases of Hodgkin and T-cell lymphoma have been reported as well. (7,20) PTL is staged based on the Ann Arbor staging criteria, and certain non-Hodgkin lymphoma subtypes. (19) Regarding PTL, the majority are B-cell lymphomas, with DLBCL the most common, accounting for 50% to 70% of all cases of PTL; rare cases of Hodgkin and T-cell lymphoma have been reported as well. (7,20) PTL is staged based on the Ann Arbor staging criteria, and certain non-Hodgkin lymphoma subtypes. (19)

Diagnosis of PTL is difficult; the disease is rare with an estimated annual incidence of 2 per 1,000,000, and clinically differentiating between PTL, lymphocytic thyroiditis, diffuse toxic goiter, organified hematoma, and anaplastic thyroid carcinoma is challenging. We preoperatively misdiagnosed the patient in this case. An enlarging thyroid nodule, usually over 1 to 3 months, is the most common clinical presentation in PTL (approximately 80%). It may be accompanied by compressive symptoms (cough, dyspnea, dysphagia, hoarseness, stridor, choking, and rarely Horner syndrome or superior vena cava syndrome) in approximately 30% of patients. Typical B symptoms of fever, night sweats, and weight loss are uncommon. In particular, DLBCL exhibits more aggressive behavior than MALT and follicular lymphomas. (7,19) This case showed typical symptoms of a rapidly growing neck mass accompanied by compressive symptoms.

Current imaging techniques (US, CT, magnetic resonance imaging, fluorodeoxyglucose positron-emission tomography, and scintigraphy) can help define the existence of a thyroid mass and provide evidence to support a diagnosis of PTL. In addition, fine-needle aspiration can be useful step in diagnosing thyroid disorders, however some reports have found that the results in PTL may not be diagnostic. (25,26) In that case, a core-needle biopsy, open biopsy, or thyroidectomy may be required along with flow cytometry or immunohistochemical staining of the specimen. (27) Histopathologically, the features that support the diagnosis of DLBCL are lack of cellular cohesion, pleomorphism with many cells showing prominent nucleoli, numerous mitotic figures, and presence of lympho-glandular bodies in the background. In immunohistochemical staining, DLBCL is usually positive for CD19, CD20, CD43, and BCL-6; MUM-1/interferon regulatory factor (IRF) 4 and FOXP1 overexpression indicate a more aggressive activated B-cell-like subgroup. (28,29) In this case, PTL was strongly suspected due to the intraoperative frozen biopsy pathological examination results, and was confirmed by postoperative pathology and immunohistochemistry.

Due to the controversy regarding the optimal treatment for PTL, there are a limited number of large randomized prospective studies. The prognosis and optimal treatment of PTL depend on the histological subtype and the stage of the disease. For DLBCL, the gold standard of treatment is multimodal therapy with R-CHOP and radiation. The role of surgical intervention in the treatment of PTL remains controversial. It is believed that the pathogenesis of the PTL is related to chronic antigen or inflammation stimulation that stimulates the B cells to secrete autoantibodies, leading to mucosa-associated lymphocyte hyperplasia, followed by lymphocyte clonal hyperplasia. Surgery may stimulate the activation of inflammatory response, and thereby cause tumor growth. However, palliative surgery may be needed to relieve severe symptoms of compression, especially in patients who do not respond rapidly to non-surgical treatment. Moreover, surgery is useful for the collection of tissue biopsies to clarify an indeterminate cytological result. Overall, PTLs have a favorable prognosis with appropriate therapy; however, DLBCL has a worse prognosis than MALT and mixed subtype due to its more aggressive clinical course. (5–7,21,27–29)

In this case, the patient underwent a palliative unilateral thyroidectomy, as she presented with compressive symptoms, which both interfered with and threatened her life, and there was no definitive preoperative diagnosis. Unfortunately, the patient died 3 weeks after surgery, due to the asphyxia caused by uncontrollable growth of recurrent tumor. We suspect that the extremely poor outcome of this patient may be related to the combination of DS and autoimmune disease, and that palliative surgery may have stimulated growth of the residual tumor. The possibility of local inflammatory response to surgery-related tissue trauma causing proliferation of lymphoma cells could not be ruled out. However, due to the patient’s severe symptoms and life-threatening nature of the tracheal compression, surgery had to be selected as the first intervention. The patient’s DS contributed to the lack of follow-up and lack of compliance with recommendation. We were nevertheless concerned about side effects of wound healing, chemotherapy and radiotherapy did not carry out on time. Whether chemotherapy has been started earlier? Overall, a multidisciplinary approach and close follow-up are needed.

This experience is from only 1 case with a poor outcome, and we hope that awareness of this entity will help oncostologists and surgeons establish timely diagnosis and treatment in the future.

Acknowledgment

We thank Editage (https://www.editage.cn/) for English language editing.
Author contributions

Conceptualization: Luyang Wei, Ning Zhao, Xiaodan Zheng, Huaxin Zhang.
Data curation: Luyang Wei.
Methodology: Luyang Wei, Ning Zhao, Yalun Li, Huaxin Zhang.
Resources: Luyang Wei, Ning Zhao, Xiaodan Zheng, Huaxin Zhang.
Supervision: Ning Zhao, Xiaodan Zheng, Zhongtao Zhang.
Validation: Zhongtao Zhang.
Writing – original draft: Luyang Wei.
Writing – review & editing: Zhongtao Zhang.

References

1. Iughetti L, Predieri B, Bruzzi P, et al. Ten-year longitudinal study of thyroid function in children with Down’s syndrome. Horm Res Paediatr 2014;82:113–21.
2. Bull MJ. Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2011;128:393–406.
3. Karlsson B, Gustafsson J, Hedov G, et al. Thyroid dysfunction in Down’s syndrome: relation to age and thyroid autoimmunity. Arch Dis Child 1998;79:242–5.
4. Popova G, Paterson WF, Brown A, et al. Hashimoto’s thyroiditis in Down’s syndrome: clinical presentation and evolution. Harm Res 2008;70:278–84.
5. Walsh S, Lowery AJ, Evoy D, et al. Thyroid lymphomas: recent advances in diagnosis and optimal management strategies. Oncologist 2013;18:994–1003.
6. Sakorafas GH, Kokkoris P, Farley DR. Primary thyroid lymphoma (correction of lymphoma): diagnostic and therapeutic dilemmas. Surg Oncol 2010;19(e124–9.
7. Alzouebi M, Goepel JR, Horsman JM, et al. Primary thyroid lymphoma: the 40 year experience of a UK lymphoma treatment centre. Int J Oncol 2012;40:2075–80.
8. Derringer GA, Thompson LD, Frommelt RA, et al. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. Am J Surg Pathol 2000;24:623–39.
9. Yang CY, Juang SS, Chuang SS, et al. Down’s syndrome with mucosa-associated lymphoid tissue, thyroid lymphoma and cerebral infarction. Chin Med (Taipei) 2000;6:3214–9.
10. Prasher V, Haque MS. Misdiagnosis of thyroid disorders in down syndrome: time to re-examine the myth? Am J Ment Retard 2003;110:23–7.
11. Claret C, Goday A, Benaiges D, et al. Subclinical hypothyroidism in the first years of life in patients with Down syndrome. Pediatr Res 2013;73:674–8.
12. Baxter RG, Larkins RG, Martin FL, et al. Down syndrome and thyroid function in adults. Lancet 1975;2:794–6.
13. Lavigne J, Sharr C, Elsharkawy I, et al. Thyroid dysfunction in patients with Down syndrome: results from a multi-institutional registry study. Am J Med Genet A 2017;173:1539–45.
14. Roizen NJ, Patterson D. Down’s syndrome. Lancet 2003;361:1281–9.
15. Aversa T, Crisafulli G, Zirilli G, et al. Epidemiological and clinical aspects of autoimmune thyroid diseases in children with Down’s syndrome. Ital J Pediatr 2018;44:39.
16. Aversa T, Lombardo F, Valenzise M, et al. Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. Ital J Pediatr 2015;41:39.
17. Pellegrini FP, Marinoni M, Frangione V, et al. Down syndrome, autoimmunity and T regulatory cells. Clin Exp Immunol 2012;169:238–43.
18. Aversa T, Salerno M, Radetti G, et al. Peculiarities of presentation and evolution over time of Hashimoto’s thyroiditis in children and adolescents with Down’s syndrome. Hormones (Athens) 2015;14:410–6.
19. Teixeira Mendes LS, Wouterspoon A. Marginal zone lymphoma: Associated autoimmunity and auto-immune disorders. Best Pract Res Clin Haematol 2017;30:65–76.
20. Widdler S, Pasieka JL. Primary thyroid lymphomas. Curr Treat Options Oncol 2004;5:307–13.
21. Graff-Baker A, Sosa JA, Roman SA. Primary thyroid lymphoma: a review of recent developments in diagnosis and histology-driven treatment. Curr Opin Oncol 2010;22:17–22.
22. Holm LE, Blomgren H, Löwhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 1995;332:601–4.
23. Pedersen RK, Pedersen NT. Primary non-Hodgkin’s lymphoma of the thyroid gland: a population based study. Histopathology 1996;28:23–32.
24. Donaldson JF, Rodriguez-Gomez IA, Parmeswaran R. Rapidly enlarging neck masses of the thyroid with Horner’s syndrome: a concise clinical review. Surgeon 2015;13:110–5.
25. Sharma A, Jasim S, Reading CC, et al. Clinical presentation and diagnostic challenges of thyroid lymphoma: a cohort study. Thyroid 2016;26:1061–7.
26. Matsuura F, Miyauchi A, Katayama S, et al. Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. Thyroid 1999;3:93–9.
27. Sarinah B, Hisham AN. Primary lymphoma of the thyroid: diagnostic and therapeutic considerations. Asian J Surg 2010;33:20–4.
28. Dralle H, Musholt TJ, Schabram J, et al. Surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch Surg 2013;398:347–75.
29. Pezzuto R, Correia PJ, Soares V, et al. Primary thyroid lymphoma: a case report and review of the literature. Ann Med Surg (Lond) 2017;13:29–33.