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Original Article

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Dyshormonogenetic Goiter: A Case Series

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Introduction: Dyshormonogenetic goiter (DG) is a rare inherited cause of congenital hypothyroidism. Although DG is intrinsically benign, chronic thyroid-stimulating hormone stimulation has been implicated as a potential tumorigenic factor. This study is a single-center experience of the clinicopathological characteristics of DG.

Methods: The hospital registry database was filtered from February 2020 to December 2025 for cases of DG. The extracted data included clinical presentation, biochemical tests, imaging findings, diagnostic approaches, management, and outcomes. Only cases with clinicopathological findings consistent with DG were included.

Results: The cohort included 15 patients (10 females, 5 males) with a median age of 17 years, ranging from 12-42 years. The disease was detected incidentally in 40.0% of cases (6/15). In total, 60.0% (9/15) had a history of congenital hypothyroidism or hypothyroidism. Ultrasonography demonstrated multinodular goiter in 93.3% (14/15), with high-risk features (TI-RADS 4 or 5) identified in 26.7% (4/15). Fine-needle aspiration cytology was performed in 4 patients, yielding Bethesda IV results in 3 cases and Bethesda II in 1 case. Histopathological examination revealed malignant neoplastic transformation in 20.0% (3/15) of cases, comprising two cases of follicular thyroid carcinomas (13.3%) and one papillary thyroid microcarcinoma (6.7%). On follow-up, all patients, except one, were euthyroid on levothyroxine.

Conclusion: Dyshormonogenetic goiter may closely mimic thyroid malignancy, and malignant transformation is also possible, which may support a role for chronic TSH stimulation as a tumorigenic stimulus, but larger multicenter studies with genetic characterization and longer follow-up are needed to define the true malignant potential of this entity.

Keywords: Dyshormonogenetic goiter; congenital hypothyroidism; thyroid neoplasms; follicular thyroid carcinoma; malignant transformation

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1. Introduction

Congenital hypothyroidism (CH) is the most common neonatal endocrine disorder, defined as thyroid hormone insufficiency at birth. Etiologically, primary CH comprises thyroid dysgenesis, reflecting aberrant glandular development, and thyroid dyshormonogenesis, denoting inherited defects of hormone biosynthesis within a structurally formed gland. The term dyshormonogenetic goiter (DG), by contrast, designates the morphological sequela of these defects [1,2]. Dyshormonogenetic goiter is a rare clinical entity first documented in the late 19th century by Pendred and Osler [3]. Unlike dysgenesis, which involves glandular agenesis or ectopia, dyshormonogenesis is characterized by an anatomically orthotopic gland. In these cases, congenital metabolic errors impede hormone biosynthesis, leading to chronic thyroid-stimulating hormone (TSH) stimulation that drives compensatory hyperplasia, goiter formation, and significant architectural distortion [4-6]. These features often mimic thyroid malignancy, creating substantial diagnostic challenges and a risk of overdiagnosis [3,4]. While the incidence of primary CH has risen to approximately 1 in 2,000 to 1 in 3,000 newborns, DG remains rare, with prevalence estimates ranging between 1 in 30,000 and 1 in 50,000 live births [1,3]. It is a genetic condition, typically inherited in an autosomal recessive pattern, arising from molecular aberrations in key proteins required for thyroid hormone biosynthesis [5,7-9]. Although DG is intrinsically benign, chronic TSH stimulation has been implicated as a potential tumorigenic factor [10-12]. This

study is a single-center experience of the clinicopathological characteristics of DG.

2. Methods

2.1 Study Design and Setting

This study was conducted in the Head and Neck Surgery Department at Smart Health Tower. The data were collected retrospectively from the department registry database for all cases that sought consultation for thyroid-related complaints from February 2020 to December 2025.

2.2 Participant Selection and Eligibility Criteria

The study eligibility criteria were limited to patients with clinicopathological findings consistent with DG (elevated TSH from childhood, orthotopic gland, characteristic histology, absence of autoimmunity by anti-TPO, family history) and with complete medical records. Therefore, cases with other thyroid abnormalities except those that were concomitant with DG, and incomplete medical records (cases with no reported clinical and pathological data) were excluded. No age, sex, or ethnicity restrictions were applied in the data retrieval.

2.3 Data Collection

Patient data were extracted from electronic medical records, radiological archives, and clinical documentation. The data included clinical presentation, biochemical tests, imaging findings, diagnostic approaches, management, and outcomes.

2.4 Data Analysis

Data entry and descriptive analysis were conducted using Microsoft Excel 2016. The distribution of the continuous variable (age) was assessed by the Shapiro-Wilk test using IBM SPSS (version 27). The variable was non-normal, so it was reported as median (quartile ranges) and range. The qualitative variables were reported as frequencies and percentages.

3. Results

This study included 15 patients with a median age of 17 years (range: 12-42 years). The cohort comprised 10 females (66.7%) and 5 males (33.3%). Two patients (Cases 4 and 5) were siblings. Six patients (40.0%) were diagnosed incidentally during routine follow-up for congenital hypothyroidism or after an incidental ultrasonography (U/S) finding, while 8 (53.3%) presented with anterior neck swelling, and 1 (6.7%) presented with facial swelling accompanied by tongue protrusion. A history of CH or hypothyroidism was documented in 9 cases (60.0%), bronchial asthma in one (6.7%), and no significant past medical history in 5 (33.3%). A family history of thyroid disease was present in 4 patients (26.7%). Goiter grading based on WHO classification [13] showed G1 in 9 cases (60.0%), G2 in 4 cases (26.7%), G3 in 1 case (6.7%), and G0 in 1 case (6.7%) (Table 1).

Preoperative biochemical assessment showed elevated TSH across the cohort, except one case (was on levothyroxine due to congenital hypothyroidism), ranging from 5.96 to >100 mIU/L (reference range: 0.35-4.94 mIU/L), with fT4 values spanning 0.55-20.63 pmol/L (reference range: 9.0-19.0 pmol/L) and Anti-TPO levels between 5.00 and 18.46 IU/mL (reference range: <34 IU/mL). Ultrasonography demonstrated multinodular goiter in 14 patients (93.3%) and a solitary nodule in 1 (6.7%), with the Thyroid Imaging Reporting and Data System (TI-RADS) category recorded as TI-RADS 2 in 1 case (6.7%), TI-RADS 3 in 11 (73.3%), TI-RADS 4 in 4 (26.7%), and TI-RADS 5 in 1 (6.7%). TI-RADS was not specified in two cases (13.3%). The largest documented thyroid lobe was the right lobe in case 6, measuring 120 × 53 × 51 mm. Ultrasound-guided fine needle aspiration cytology was performed in 4 patients, yielding Bethesda IV results in 3 cases and Bethesda II in 1 case (Table 2).

All patients underwent total thyroidectomy, and the rationale included high goiter grading (cases 3,6,8,9) and congenital hypothyroidism with compressive symptoms/inability to exclude malignancy (cases 1-4,11-13), TI-RADS category > 3 (cases 2,6,7,15), Bethesda ≥ IV (cases 6 to 8), and nodular sizes greater than 2.5 cm on U/S (cases 3,6-11,13-15) and positive family history for thyroid cancer and dyshormonogenesis (cases 4,5). Histopathological examination revealed malignant neoplastic transformation in 20.0% (3/15) of cases, comprising two cases of follicular thyroid carcinomas (13.3%) and one papillary thyroid microcarcinoma (6.7%). On microscopic examination, sections showed irregularly sized thyroid follicles with scant colloid and areas of empty lumina, with background fibrosis and multiple adenomatoid nodules, and focal marked nuclear atypia (Figure 1). The two patients with follicular thyroid carcinoma underwent radioactive iodine therapy, and the other case of papillary thyroid microcarcinoma remained under regular follow-up. Postoperatively, all patients were alive and clinically stable on levothyroxine doses of 100-150 µg daily. TSH values, 8 weeks after starting replacement therapy, were within the reference range for 14 patients (0.43-4.59 mIU/L), while one patient had a slightly elevated level of 5.74 mIU/L (reference range: 0.35-4.94 mIU/L). The follow-up period ranged from 1 year to 4 years (Tables 2 & 3).

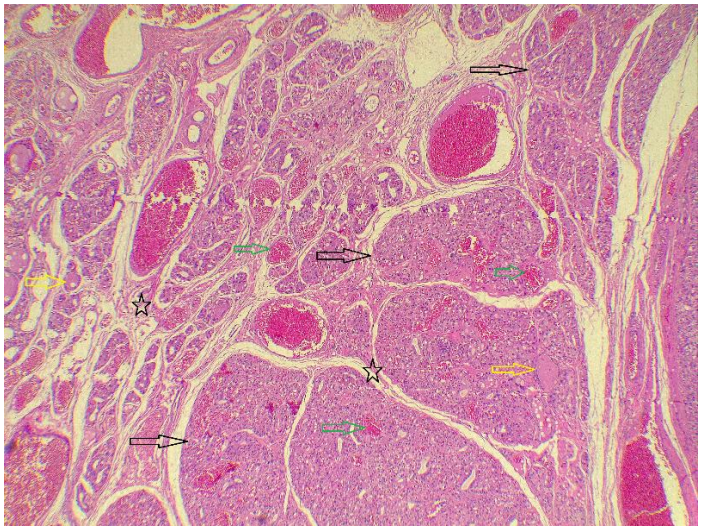

Figure 1. The section shows nodules of thyroid follicles (dark arrows), most of them composed of empty follicles, while a few others contain little colloid material (yellow arrows) and are separated by fibrous bands (dark stars), with the presence of numerous different-sized vascular proliferations (green arrows). Hematoxylin and Eosin stain 10X .

Table 1. Demographic and clinical characteristics of patients

Case No.	Age (Y)	Gender	History						Clinical Thyroid Examinations
			Presentation	PMH	PSH	FHX	Medication Hx	Smoking	
Case 1	17	M	Thyroid check-up	Congenital Hypothyroidism	None	None	T4 100 µg	No	G0
Case 2	16	F	Neck swelling	Congenital Hypothyroidism	None	Thyroid disease, DM, HTN	T4 100 µg	No	G2
Case 3	16	M	Neck swelling	Congenital Hypothyroidism	None	None	T4 75 µg	No	G2
Case 4	12	F	Thyroid check-up	Congenital Hypothyroidism	None	Dyshormonogenesis, Papillary Thyroid Carcinoma	T4 75 µg	No	G1
Case 5	15	F	Thyroid check-up	Bronchial Asthma	None	Dyshormonogenesis, Papillary Thyroid Carcinoma	None	No	G1
Case 6	32	F	Thyroid check-up	None	None	None	None	No	G3
Case 7	26	M	Thyroid check-up	None	None	None	None	No	G1
Case 8	21	F	Neck swelling	None	None	None	None	No	G2
Case 9	21	F	Facial swelling, Tongue protrusion	None	None	None	None	No	G2
Case 10	17	F	Neck swelling	None	None	None	None	No	G1
Case 11	16	M	Thyroid check-up	Congenital Hypothyroidism	None	None	T4 100 µg	No	G1
Case 12	18	M	Neck swelling	Congenital Hypothyroidism	Eye surgery	Hypothyroidism	T4 100 µg	No	G1
Case 13	14	F	Neck swelling	Congenital Hypothyroidism	None	None	T4 100 µg	No	G1
Case 14	32	F	Neck swelling	Hypothyroidism	None	None	T4 75 µg	No	G1
Case 15	42	F	Neck swelling	Hypothyroidism	None	None	T4 75 µg	No	G1

***Abbreviations. No.**, Number; **Y**, Year; **M**, Male; **F**, Female; **PMH**, Past Medical History; **PSH**, Past Surgical History; **FHX**, Family History; **DM**, Diabetes Mellitus; **HTN**, Hypertension; **Hx**, History; **T4**, Levothyroxine; **µg**, Microgram; **G**, Grade (of Goiter).*

Table 2. Diagnosis, management, and outcomes of patients

Case No.	Biochemical Profile			Neck Ultrasound				FNAC	Surgical Procedure	HPE	Postoperative Management	Postoperative TSH (mIU/L)	Follow-Up Status	Post-operative follow-up duration (years)
	TSH (mIU/L)	fT4 (pmol/L)	Anti-TPO (IU/mL)	Findings	Right Lobe Size (mm)	Left Lobe Size (mm)	Nodule Characteristics							
Case 1	67.59	10.65	7.89	Thyroiditis	65 × 20 × 18	60 × 20 × 18	Multinodular Goiter; 14 × 7 mm nodule at the inferior junction of the Right Lobe and isthmus.	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	3	Alive, Euthyroid	1
Case 2	100.00	0.55	5.00	Thyroiditis	40 × 13 × 12	37 × 13 × 12	Multinodular Goiter. Right Lobe: 18 × 8 mm well-defined hypoechoic nodule with punctate echogenic foci (ACR TI-RADS 5); 8 × 4 mm (ACR TI-RADS 4); 2 × 2 mm well-defined hypoechoic nodule (ACR TI-RADS 4). Left Lobe: 11 × 8 mm nodule with perinodular vascularity but no intra nodular vascularity (ACR TI-RADS 4).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	0.9	Alive, Euthyroid	3
Case 3	>100.00	4.36	6.54	Thyroiditis	77 × 33 × 32	70 × 26 × 21	Multinodular Goiter. Right Lobe: Well-defined, predominantly solid, iso- to hyperechoic nodule (43 × 30 ×25 mm) in upper-mid third (ACR TI-RADS 3); two similar nodules (14 × 13 × 12 mm in mid-third; 21 × 14 × 12 mm in lower-third). Left Lobe: Two small nodules, largest 5 × 3 mm (ACR TI-RADS 2).	Not performed	Total Thyroidectomy	DG	T4 100 µg	4.05	Alive, Euthyroid	1
Case 4	41.59	9.75	12.22	Thyroiditis	65 × 23 × 20	60 × 22 × 20	Multinodular Goiter. Right Lobe: 20 × 16 × 14 mm nodule (ACR TI-RADS 3). Left Lobe: 17 × 14 × 10 mm nodule (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG	T4 100 µg	4.37	Alive, Euthyroid	4
Case 5	20.89	12.08	11.11	Multinodular Goiter	65 × 15 × 14	60 × 13 × 13	Multinodular Goiter. Right Lobe: 11 × 8 × 6 mm nodule (ACR TI-RADS 3). Left Lobe: Largest nodule 11 × 7 × 5 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	0.43	Alive, Euthyroid	2

Case 6	10.67	7.65	18.46	Multinodular Goiter	120 × 53 × 51	110 × 43 × 35	Multinodular Goiter. Right Lobe: 40 × 32 × 30 mm (ACR TI-RADS 3) and 29 × 20 × 18 mm (ACR TI-RADS 4). Left Lobe: Largest nodule 22 × 18 × 17 mm (ACR TI-RADS 3) and 16 × 15 × 12 mm (ACR TI-RADS 4).	Bethesda IV	Total Thyroidectomy	Follicular Thyroid Carcinoma with Complete capsular and vascular (at least two vessels) invasion arising from DG	T4 100 µg	5.74	Alive, No Recurrence with slightly elevated TSH	3
Case 7	100.00	2.52	13.10	Multinodular Goiter	50 × 17 × 15	65 × 44 × 34	Multinodular Goiter. Right Lobe: 10 × 6 × 5 mm nodule (ACR TI-RADS 4). Left Lobe: Large (57 × 41 × 29 mm), well-defined, regular, predominantly solid nodule with macrocalcification and increased perinodular/intranodular vascularity (ACR TI-RADS 4).	Bethesda IV	Total Thyroidectomy	Follicular Thyroid Carcinoma with Complete capsular and vascular (at least 6 vessels) invasion arising from DG	T4 100 µg	3.26	Alive, Euthyroid	1
Case 8	53.25	9.75	7.20	Thyroiditis	60 × 32 × 25	43 × 14 × 14	Solitary Nodule. Well-defined, regular surface, solid nodule (37 × 29 × 23 mm) occupying most of the gland.	Bethesda IV	Total Thyroidectomy	Follicular Adenoma arising from DG	T4 150 µg	0.91	Alive, Euthyroid	1
Case 9	47.41	8.30	5.40	Thyroiditis	70 × 26 × 24	80 × 27 × 25	Multinodular Goiter. Right Lobe: Largest nodule 19 × 14 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 31 × 22 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 150 µg	4.43	Alive, Euthyroid	3
Case 10	5.96	17.86	9.13	Multinodular Goiter	77 × 40 × 37	80 × 42 × 38	Multinodular Goiter. Right Lobe: Largest nodule 36 × 31 × 28 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 29 × 25 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	3.39	Alive, Euthyroid	2
Case 11	0.67	20.63	5.40	Multinodular Goiter	95 × 45 × 40	77 × 41 × 33	Multinodular Goiter. Right Lobe: Largest nodule 32 × 25 × 24 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 25 × 22 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	4.39	Alive, Euthyroid	2
Case 12	16.06	20.01	5.09	Multinodular Goiter	60 × 24 × 21	56 × 20 × 18	Multinodular Goiter. Right Lobe: Largest nodule 22 × 16 × 14 mm	Bethesda II	Total Thyroidectomy	Papillary Thyroid Microcarcinoma, Conventional	T4 100 µg	4.59	Alive, Euthyroid	

							(ACR TI-RADS 3). Left Lobe: Largest nodule 18 × 10 mm (ACR TI-RADS 3).			Subtype (0.5 cm), Unifocal, Left Thyroid Lobe, without Extrathyroidal Extension, Lymphovascular or Perineural Invasion, arising in DG with Multiple Bilateral Adenomatoid Nodules (pT1aN0).				1
Case 13	5.96	17.86	7.13	Multinodular Goiter	80 × 41 × 36	100 × 60 × 44	Multinodular Goiter. Right lobe: Largest nodule 40 × 35 × 27 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 36 × 28 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	2.59	Alive, Euthyroid	4
Case 14	>100	4.59	15.60	Multinodular Goiter	67 × 32 × 29	60 × 29 × 27	Multinodular Goiter. Right Lobe: Largest nodule 34 × 30 × 23 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 26 × 20 × 13 mm (ACR TI-RADS 3).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	2.59	Alive, Euthyroid	3
Case 15	14.05	7.99	10.02	Multinodular Goiter	80 × 44 × 35	70 × 30 × 24	Multinodular Goiter. Right Lobe: Largest nodule 39 × 23 × 20 mm (ACR TI-RADS 3). Left Lobe: Largest nodule 14 × 10 × 8 mm (ACR TI-RADS 4).	Not performed	Total Thyroidectomy	DG with multiple adenomatoid nodules	T4 100 µg	1.09	Alive, Euthyroid	2

***Abbreviations. No**., Number; **TSH,** Thyroid Stimulating Hormone; **mIU/L,** Milli-international units per liter; **fT4**, Free Thyroxine; **pmol/L**, Picomoles per liter; **Anti-TPO**, Anti-thyroid Peroxidase Antibody; **IU/mL**, International units per milliliter; **mm**, Millimeter; **ACR**, American College of Radiology; **TI-RADS**, Thyroid Imaging Reporting and Data System; **FNAC**, Fine Needle Aspiration Cytology; **Bethesda IV**, Suspicious for Follicular Neoplasm; **HPE**, Histopathological Examination; **Bethesda II**, Benign. **DG**, Dyshormonogenetic Goiter; **µg**, Microgram; **T4**, Levothyroxine.*

Table 3. Summary of patient characteristics and diagnosis

Variable	Frequency (n)/Median (Q1-Q3)/Range	Percentage (%)
Gender		
Male	5	33.3%
Female	10	66.7%
Age (Yrs)		
Median (Q1-Q3)	17 (16-26)	
Range	12-42	
Clinical Presentation		
Incidental finding	6	40.0%
Neck swelling	8	53.3%
Facial swelling/Tongue protrusion	1	6.7%
Past Medical History		
Congenital Hypo/Hypo	9	60.0%
Bronchial Asthma	1	6.7%
No significant history	5	33.3%
Clinical Thyroid Examination		
G 0	2	13.3%
G 1	9	60.0%
G 2	3	20.0%
G 3	1	6.7%
Family History of Thyroid Disease		
Positive	4	26.7%
Negative	11	73.3%
Ultrasound Features		
Multinodular Goiter	14	93.3%
Solitary nodule	1	6.7%
ACR TI-RADS Score Per Case*		
TI-RADS 2	1	6.7%
TI-RADS 3	11	73.3%
TI-RADS 4	4	26.7%
TI-RADS 5	1	6.7%
Not specified	2	13.3%
Other pathologies besides DG		
Multiple adenomatoid nodules	10	66.7%
Follicular Thyroid Carcinoma	2	13.3%
Papillary thyroid microcarcinoma	1	6.7%
Follicular Adenoma	1	6.7%
None	2	13.3%

*****Each case may have lesions with different TI-RADS*

***Abbreviations. N**, (number of patients in a specific category); **Yrs**, Years; **G**, Grade (of goiter); **ACR**, American College of Radiology; **TI-RADS**, Thyroid Imaging Reporting and Data System; **Hypo**, Hypothyroidism; **DG**, Dyshormonogenetic Goiter.*

4. Discussion

The clinical presentation of DG is classically documented as a neonatal or infantile condition, often manifesting immediately after birth. Previous reports have documented neonatal presentations with clinically significant airway compression, including a case involving a 4-day-old infant, as well as large cervical masses detected as early as 11 hours after birth [2,14]. Additionally, fetal goiters may cause complications such as polyhydramnios in utero [2]. In contrast to these findings, the diagnosis in this series was established at a median age of 17 years in accordance with the clinicopathological study by Ghossein et al., which reported a median age of approximately 16 years at surgery [15]. This delayed presentation aligns with reports of adolescents and young adults who remain undiagnosed until metabolic demands peak, as in cases of a 19-year-old male and a 10.5-year-old boy recently reported [7,16]. This spectrum of early-onset disease includes genetically defined cases, such as siblings with fetal goiters caused by compound heterozygous *TPO* gene mutations, which can also affect long-term neuropsychological outcomes [17]. The exclusivity of adolescent and adult patients in this case series (≥12 years old) corroborates observations from other resource-limited settings, where diagnosis is frequently delayed by over a decade, supporting the hypothesis of "compensated dyshormonogenesis", which permits subclinical progression into adulthood [4].

The clinical presentation observed in this study differs markedly from the acute manifestations seen in neonates. While several reported neonatal cases present with life-threatening stridor or severe neck extension [4,8,15], the clinical picture observed in the present study was predominantly insidious. Overall, 40.0% of the patients were identified incidentally, a finding that contrasts with case reports from India, where older children consistently presented with overt neck swelling and mechanical symptoms like dyspnea [3,4]. However, this high rate of incidental detection aligns with a study, where siblings of index patients were found to have goiters despite being clinically asymptomatic [10]. The absence of acute symptoms in a subset of the present cases, despite significant glandular enlargement in some, reinforces the insidious nature of partial enzymatic defects, which can allow patients to remain clinically compensated for years before structural changes necessitate evaluation [7].

Radiological evaluation often reveals features overlapping significantly with thyroid malignancy, complicating risk stratification. Literature indicates that benign dyshormonogenetic nodules frequently exhibit solid composition and hypoechogenicity, characteristics traditionally associated with malignancy, often leading to high TI-RADS scores [6]. In this study, U/S identified several nodules with high-risk features, which were classified as TI-RADS 4 or 5. This rate of suspicious findings is similar to pediatric cases and supports the decision for total thyroidectomy to rule out cancer [4]. Although benign features like a hypoechoic "halo" rim have been reported, the heterogeneous presentation underscores the diagnostic limitations of U/S in DG, where chronic TSH-driven hyperplasia creates architectural distortions that mimic neoplastic processes [6].

Histopathological evaluation of DG poses significant diagnostic challenges due to the profound architectural and cellular pleomorphism induced by chronic TSH stimulation. Characteristic features such as hypercellularity, nuclear atypia, and scant colloid, as described in the literature, can easily lead to a misdiagnosis of follicular or papillary thyroid carcinoma [3]. Furthermore, the presence of mitotically active follicular nodules has been reported to raise suspicion for poorly differentiated carcinoma, necessitating careful differentiation [18]. In the present study, histological confirmation of DG displayed irregular thyroid follicles with scant colloid, extensive background fibrosis, and multiple adenomatoid nodules. These findings align with observations that chronic TSH

stimulation leads to a spectrum of proliferative changes, ranging from benign hyperplasia to lesions with uncertain malignant potential [6].

Beyond diagnostic mimicry, DG carries a potential risk of carcinogenesis. Although intrinsically benign, the chronic, high-intensity TSH stimulation serves as a potent proliferative driver that may promote mutagenesis over time. This risk is further amplified in patients with coexisting genetic syndromes; for instance, the combination of a *TPO* mutation with a *PTEN* mutation in Bannayan-Riley-Ruvalcaba syndrome may play a synergistic role in the development of multinodular goiter and increase the risk of malignant transformation [19]. Although rare, associations exist between dyshormonogenesis and the development of malignancies, including papillary thyroid carcinoma with lung metastasis and follicular thyroid carcinoma in patients with *TPO* mutations [20,21]. More aggressive outcomes, such as anaplastic thyroid cancer, have also been reported in association with specific *TG* gene mutations [11]. In this series, a malignant neoplastic transformation rate was observed, with 20.0% of patients diagnosed with thyroid cancer, including two cases of follicular thyroid carcinoma and a case of papillary thyroid microcarcinoma. This incidence may support the hypothesis that prolonged TSH elevation, potentially coupled with specific genetic backgrounds such as germline *DUOX2* mutations, contributes to tumor progression [12].

The genetic landscape of thyroid dyshormonogenesis is highly heterogeneous, involving pathogenic variants in genes encoding key enzymes and transporters. While *TPO* mutations are traditionally classified as a primary cause of total iodide organification defects, recent large-scale cohorts have elucidated *DUOX2* variants as a frequent etiology associated with a broad phenotypic spectrum [1,5,9]. Additionally, specific *TG* gene mutations causing intracellular transport defects can lead to goiter formation even with normal TSH levels [22]. Although molecular genetic testing was not performed in this series, a positive family history of thyroid disease in 26.7% of cases and having 2 sibling cases may be consistent with the predominantly autosomal recessive inheritance pattern typical of these metabolic disorders [5]. The clinical and histopathological findings strongly suggest underlying defects in the hormone biosynthetic pathway similar to those described in genetically characterized cohorts [1,9].

Management strategies for DG are dictated by the age of presentation and the severity of glandular enlargement. While early levothyroxine replacement in neonates can successfully reduce goiter size and relieve airway compression, the structural alterations characterized by dense fibrosis and multiple adenomatoid nodules in older patients are likely irreversible with medical suppression alone [2,3,21]. Consequently, total thyroidectomy served as the definitive management for all patients in this series, addressing both compressive symptoms due to neck swelling and the need to rule out malignancy in suspicious nodules. This approach is supported by recent literature advocating for surgery when conservative management fails or when malignancy cannot be excluded [4]. Postoperative outcomes were favorable, with nearly all patients achieving a stable euthyroid status on replacement therapy. Despite the limitation regarding genetic analysis (too costly for patients), this study highlights the significant risk of neoplastic transformation in patients with delayed diagnosis, underscoring the necessity for vigilant surveillance and a lower threshold for surgical intervention [21]. Other limitations included the study design, the relatively short follow-up period, and the inability to retrieve histopathological images for cases associated with malignancy, which limited further characterization of the disease and may have reduced the generalizability of the findings.

5. Conclusion

Dyshormonogenetic goiter may closely mimic thyroid malignancy, and malignant transformation is also possible, which may support a role for chronic TSH stimulation as a tumorigenic stimulus, but larger multicenter studies with genetic characterization and longer follow-up are needed to define the true malignant potential of this entity.

Declarations

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Ethical Approval: Not applicable.

Consent for Participation: Not applicable.

Consent for Publication: Informed consent for the publication of anonymized clinical data and images was obtained from all patients (or their legal guardians, where applicable).

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Authors' Contributions: AMS, AMA and ANQ: Major contributors to the conception of the study, as well as the literature search for related studies, and manuscript writing. AAQ, SHH, SAN, SHA, MHA, MLA, OAA, AOH, MHR, DAK, HAA, SMJ: Literature review, critical revision of the manuscript, and processing of the tables.

Use of AI: ChatGPT (GPT-5.5, OpenAI) was used to assist with language refinement and improve the overall clarity of the manuscript. All content was thoroughly reviewed and approved by the authors, who bear full responsibility for the final version.

Data Availability Statement: All data generated or analyzed during this study are included in this published article. Further enquiries can be directed to the corresponding author.

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