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Solid Variant of Papillary Thyroid Carcinoma in a 15-Year-Old Boy: Diagnostic Utility of Immunohistochemical Panel

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Abstract:
We present case of 15-year-old boy having solid-trabecular histological type in low-differentiated variant of PTC. The interest in the described case is also determined by the fact that in the preoperative examination of the patient thyroid nodular goiter and Hürthle cell adenoma of indefinite atypia by FNA (Bethesda III) was fixed, no PTC-induced changes and family history and radiation exposure was absent. In fact, we had three clinical-morphological versions: 1. Hürthle cell adenoma; 2. Nodular goiter; 3. PTC solid-trabecular variant. Differential diagnosis between medullary and anaplastic carcinomas should to be made by using of histological and immunohistochemical methods. A multicomponent immunohistochemical study have shown the high activity of TTF1, Cyclin D1 and thyroglobulin in combination with the activity of E-CAD indicating on the solid-trabecular variants of PTC, the epithelial phenotype and the transcription activity of thyroid-specific proteins were preserved, which is significant. Coordinated activity of TTF1 and Cyclin D1 is manifested by tumor tissue growth and differentiation and this phenomenon explains the tumor spread isolated characters and no local metastasis, which is one of highlight of our case. Therefore, the presented case does not have any features of undifferentiated carcinoma**.**

Keywords: Solid variant, 15-year-old boy, Immunohistochemical panel.

INTRODUCTION

Papillary Thyroid Carcinoma (PTC) is the most common tumor of thyroid gland, about 80% of all malignant formation of thyroid gland. Besides the most common follicular and tall cell variants, PTC is one of the following histological options from Solid Variant of PTC (SVPTC), which is rare about 1-3% of PTC options and at the same time is most common in children. This option is not well studied. SVPTC tumor parenchyma present solid-trabecular components and the neoplastic cells revealed hypercellular nests with PTC's cytological patterns. SVPTC is first described by Carcangiu et al. in 1985. Later Nikiforov Y. et al. discussed SVPTC high rate (37%) in children and young people as a result of Chernobyl's nuclear accident. SVPTC has a less good prognosis than classical papillary carcinoma including shorter survival rate, however, much better than a low differentiated and antaplastic carcinomas. Therefore, a morphological assessment of unclear histological criteria of this variant is important to avoid more aggressive diagnosis and recommended total thyroidectomyfor recurrenceprevent.

Case Presentation

A 15-year-old boy was admitted for an anterior neck mass and discomfortduring swallowing. He had no history of prior radiation to the head and neck and no known family medical history on endocrine disease. Onphysical examination, patient was medically stable with a blood pressure

of 125/60mmHg, pulse of 97 beats per minuteand a temperature of 36. 5°C.The thyroid gland moved upon swallowing.Thyroid gland of dense-elastic consistency. Left lobe – the nodule was well demarcated and measuredabout3.0 cm in size. It was not adherent to any adjacent structures. Right lobe and isthmus appeared to be normal.

Laboratory Results:

serum levels of free triiodothyronine, free thyroxine and thyrotropin, Vitamine D were within normal value range. Also, thyroglobulin and anti-thyroglobulin were negative. Ultrasound examination of the neck showed irregular hypoechoic nodule in the left lobe measuring 17X20X28 mm, with peri- and intranodular vascularization at colour-Doppler examination. The right thyroid lobe appeared normal. On the left side of the neck, in the middle third, behind the sternocleidomastoid muscle, there are two lymph nodes with a 7 mm length. Hilus slightly preserved and echogenic.From the left lobe of the thyroid gland caudally paratracheal lymph nodes were observed measuring 7 mm, 8 mm. and 7 mm. in size. Hilus slightly preserved and echogenic. From the right lobe of the thyroid gland caudally paratracheal lymph nodes were observed measuring 5 mm, 7 mm.and 7 mm in size. Hilus slightly preserved and echogenic (Fig. 1).

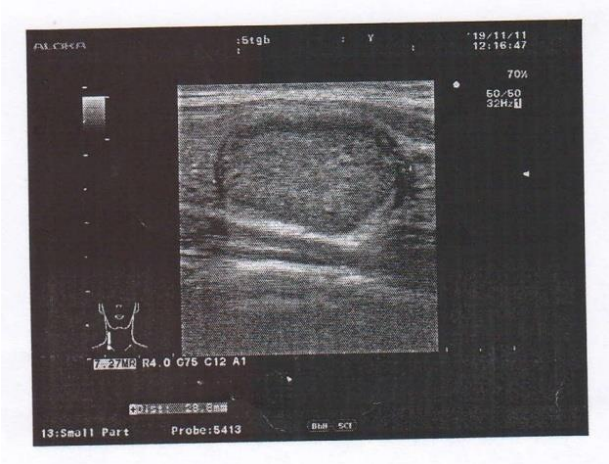


Figure 1. Thyroid ultrasound image showing irregular hypodense lesion in the enlarged left lobe (Aloka SSD alfa 6-4D).

Patient was screened for multiple endocrine neoplasia with negative results.

Thyroid aspiration (FNA) cytology documented lymphoplasmocytic infiltration, follicular cells hyperplasia, Hurthle cells metaplasia, atypia of undetermined significance by Bethesda Category III. Based on both cytopathological findings and ultrasound examination preoperative diagnosis was Nodular goiter E04.1 Patient underwent a total thyroidectomy, without neck dissection. Thyroid gland elastic consistency, in the lower pole of the large left lobe nodular formation up to 2 cm in size was detected. Right lobe in normal consistence.

MATERIALS AND METHODS

Present case was reviewed and deemed exempt from written informed parents' consent by the Ethics committee and Board of medical sciences at Tbilisi State University based on Helsinki-Ethical Principles Declaration for Medical Research [7].

Histological and Immunohistochemical Analyses

Gross examination showed a total thyroidectomy excised specimen weighed 88 g, with the right lobe measuring 45×20×30 mm, left lobe 60×30×20 mm and isthmus 30×20×11 mm.

Surgical specimens from left and right lobe and isthmus were fixed in 10% buffered formalin solution for 24 h and embedded in paraffin as routine. For histological examination 5-7 µm thick sections were stained with hematoxylin and eosin (H&E). Immunohistochemical (IHC) staining was performed on Formalin-fixed paraffin embedded (FFPE) tissue sections with antibodies against the following markers (Tab.1) Hematoxylin is used for nuclei counterstaining. Appropriate positive and negative controls were included for each reaction. All procedures were carried out in compliance with antibodies manufacturers' protocols.

Table 1. Antibodies sources and manufacturers

Primary antibody	Clone	Dilution	Source
Cytokeratin cocktail AE1/AE3	AE-1/AE-3	1:200	BioGenex, San Ramon, CA, USA
Chromogranin A	CGA/413+CHGA/777+CHGA/804	1:2000	BioGenex
Thyroglobulin	Polyclonal	1:8000	Dako, Denmark
Calcitonin	SKU: AN926GP	1:500	BioGenex
CEA	SKU: FG-365M-GP	1:20 000	BioGenex
S100	RTU-S100p	1:200	Biogenex
TTF1	SPT24	1:200	Leica, UK
Cyclin D1	P2D11F11	1:40	Leica, UK
CD56	CD564	1:50	Leica, UK
HBME-1	HBME-1	1:50	Dako, Denmark
Ki67	MIB-1	1:500	Dako, Denmark
E-CAD	NCH-38	1:200	Dako, Denmark

Statistical Analysis

The intensity of staining was assessed semi-quantitatively by the evaluation of 150 cells in each high magnification field. The staining was regarded as positive in the case of nuclear/membrane expression. The results were expressed in – and + (-: no staining; -/+: staining present in 0–30% of cells, +: in 31–60% of cells, ++: in 61–90% of cells, and +++: in more than 90% of cells) (Figure 3).

RESULTS AND DISCUSSION

Multiple tissue sections were taken for microscopic analysis. On histological examination: a nodule is seen in the left lobe surrounded by a fibrous capsule constructed of compactly arranged rounded and in some places with slightly elongated cells. The neoplastic follicular cells are in trabecular arranged or solid nests separated by fibrohyaline eosinophilic stroma. Tumor cells nuclei were large, optically clear, some irregular pleomorphic counterstain nuclei demonstrate grooves with distinct nucleolemma. Most of cells are located in perivascular area and initially reported as undifferentiated carcinoma with focal papillary area. Neither mitotic activity and nor area of necrosis are seen. The well-defined fibrous capsule was determined and separated neoplastic areas from the nonneoplastic parenchyma, which often present in PTC. It also showed foci of folicullar cells hyperplasia, so-called stratification area (Figure. 2). Right lobe of the thyroid gland presents micro- and normofollicular structure.

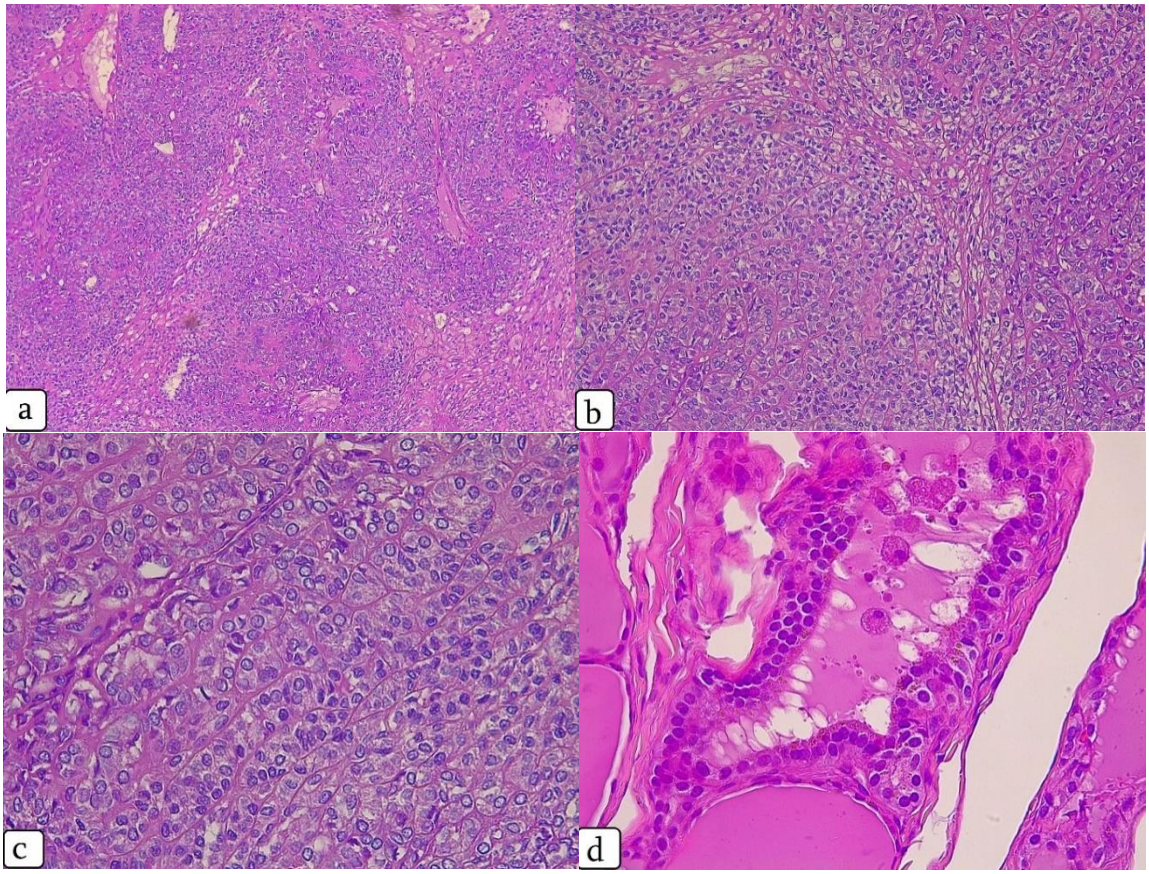


Figure 2. Solid variant of papillary thyroid carcinoma (SVPTC). H&E staining. a - The solid nests surrounded by fibrohyline stroma; no papillary growth is present. b - The trabecular pattern of neoplastic cells. b, c – so-called ground-glass appearance of nuclei having classical nuclear features of PTC. d – Stratification area of follicular neoplastic cells with extensive fibrosis. a – X100; b – X200; c, d – X400.

Differential Diagnosis

Collision of nonclassical nuclear features of PTC, solid nest and trabecullar arrangement of tumor cells, rarely reported undifferentiated carcinoma in children substantiated immunohistochemical examination in this case. Moreover, preoperative diagnosis was nodular goiter and FNA revealed Hurthle cells metaplasia and atypia of undetermined significance by Bethesda Category III.

Immunohistochemical Study Results

Immunohistochemical staining showed the tumour cells were positive for Thyroglobulin (Tg), thyroid transcription factor-1 (TTF-1), Cyclin D1, E-CAD, Cytokeratin AE1/AE3, Ki-67 (Figure 3) and unequivocally negative expression of Calcitonin, Chromogranin A, S100 protein, HBME-1, CEA (carcinoembryonic antigen) (Figure 5). However, CD56 was positive in nonneoplastic and negative for neoplastic area, which is characterize for this antibody (Figure 5 d). Among the positive immunohistochemical results is noteworthy the strong cytoplasmic immunepositive reaction of thyroglobulin (Tg) in follicular cells, diffuse nuclear positivity of thyroid transcription factor 1 (TTF1) in SVPTC cells and diffuse positive expression of E-CAD in tumor cells, markedly reduced staining in the nonneoplastic area. High diffuse Cyclin D1 staining was in SVPTC cells nuclei. Focal immunepositive reactivity of cytokeratin AE1/AE3 was observed in the SVPTC trabecular area. As for the Ki-67 labeling index in tumor cells is very low (≈3%) (Figure 4).

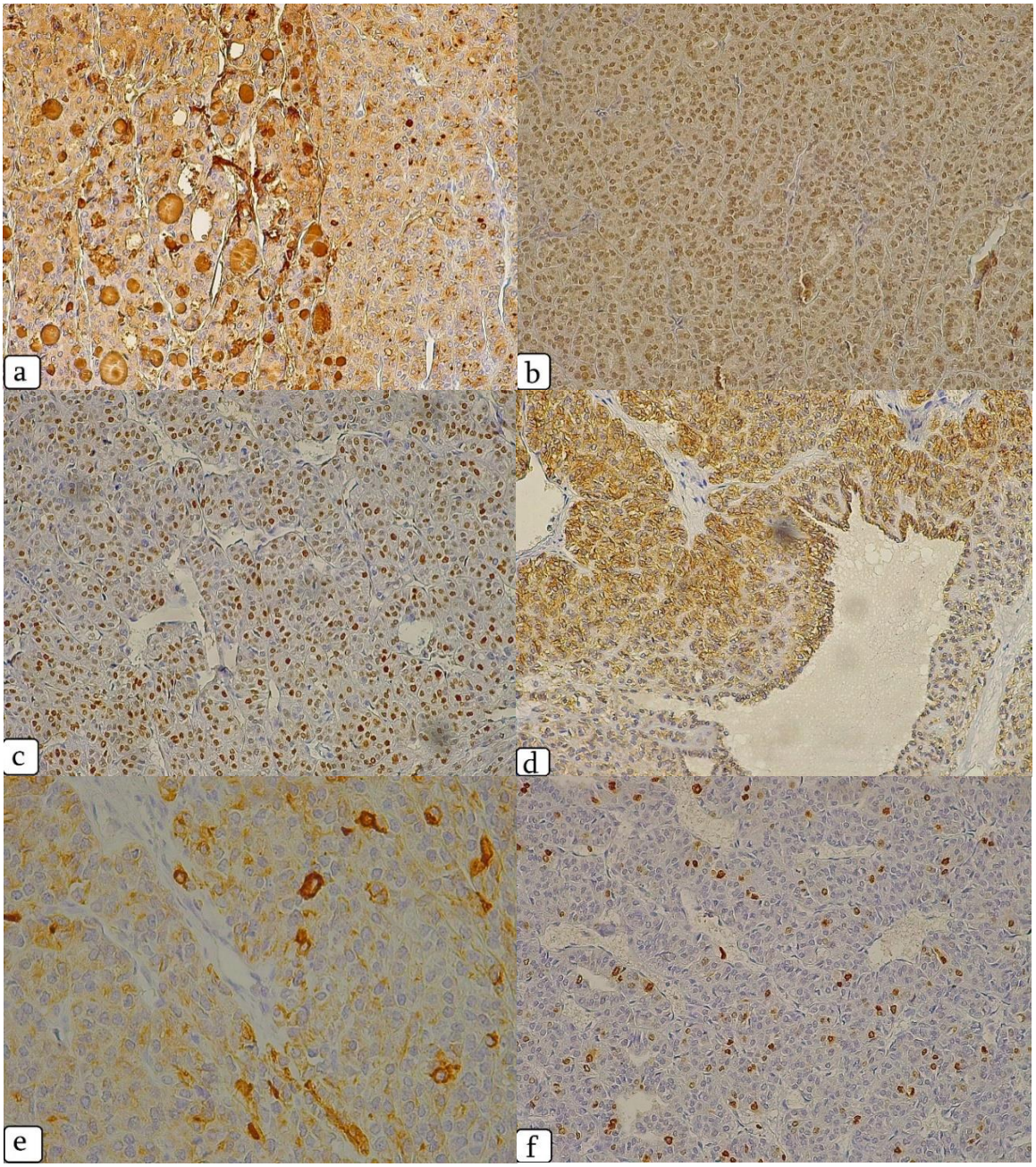


Figure 3. The positive immunohistochemical results for SVPTC case. a – Strong cytoplasmic immunopositivity of Thyroglobulin (Tg) infollicular cells. b – Diffuse nuclear positivity of Thyroid transcription factor 1 (TTF1) in SVPTC cells. c – Diffuse higher Cyclin D1 expression in SVPTC cells nuclei. d – Diffuse positive expression of E-CAD in tumor cells, note the markedly reduce staining in nonneoplastic area. e – Focal immunopositivity of Cytokeratin AE1/AE3 in SVPTC trabecular area. f – The Ki-67 labeling index in tumor cells is very low (3%). Immunoperoxidase reaction. a-d, f – X200; e – X400.

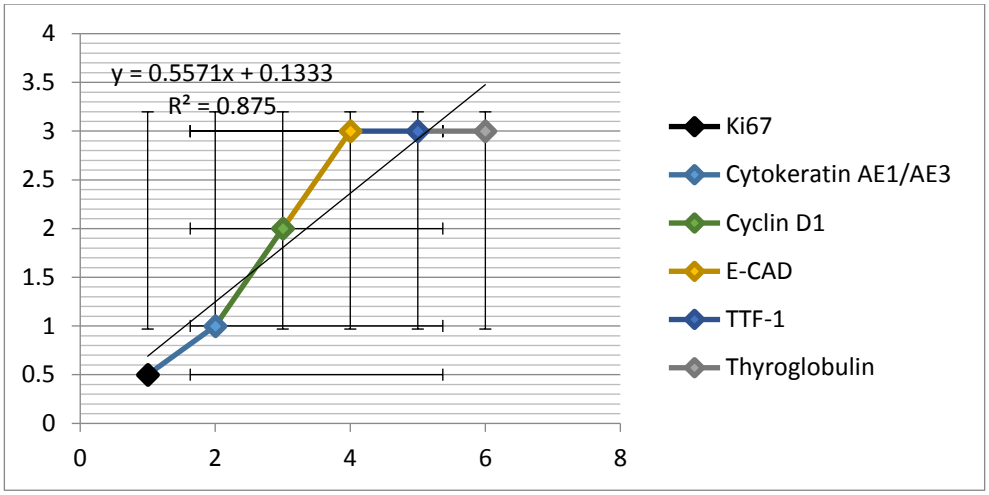
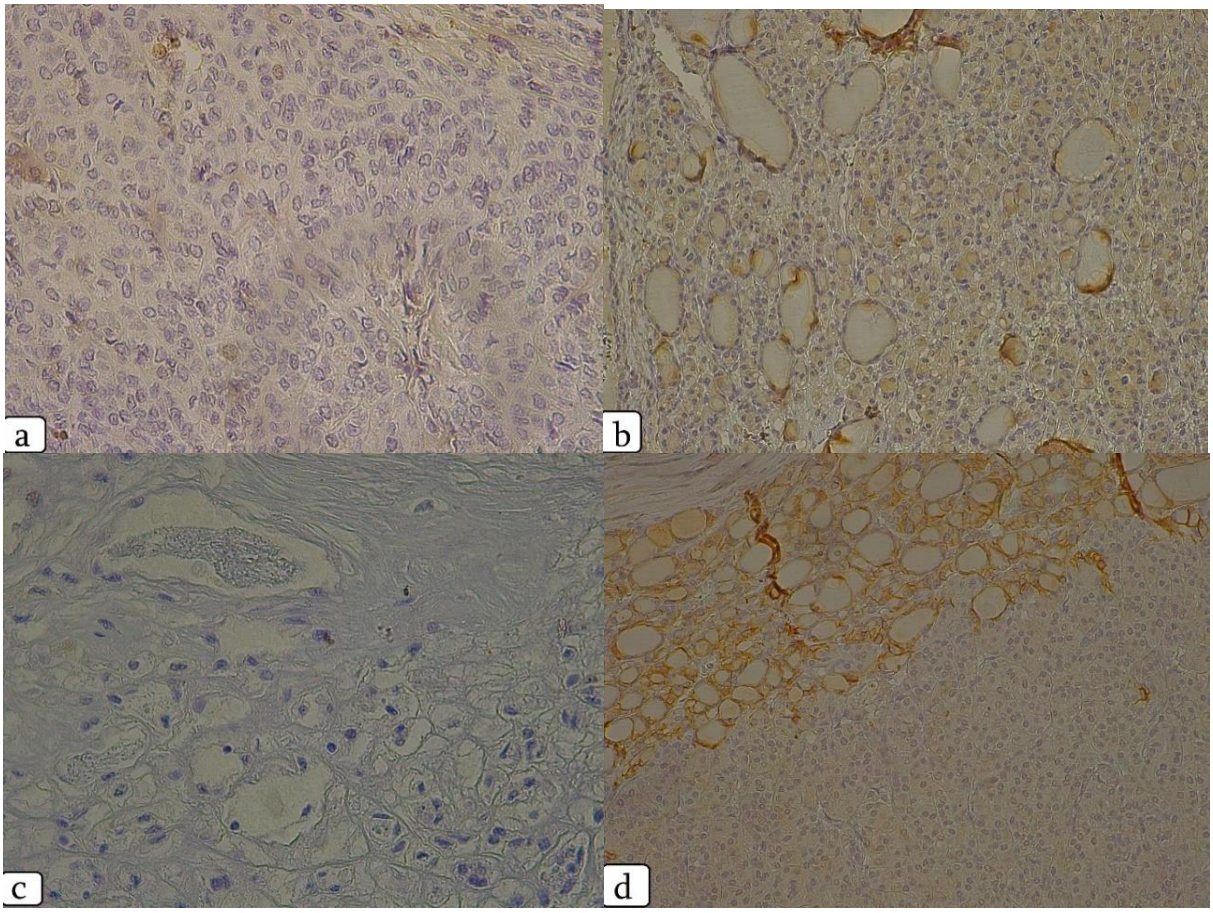


Figure 4. Immunostaining positive results for SVPTC case



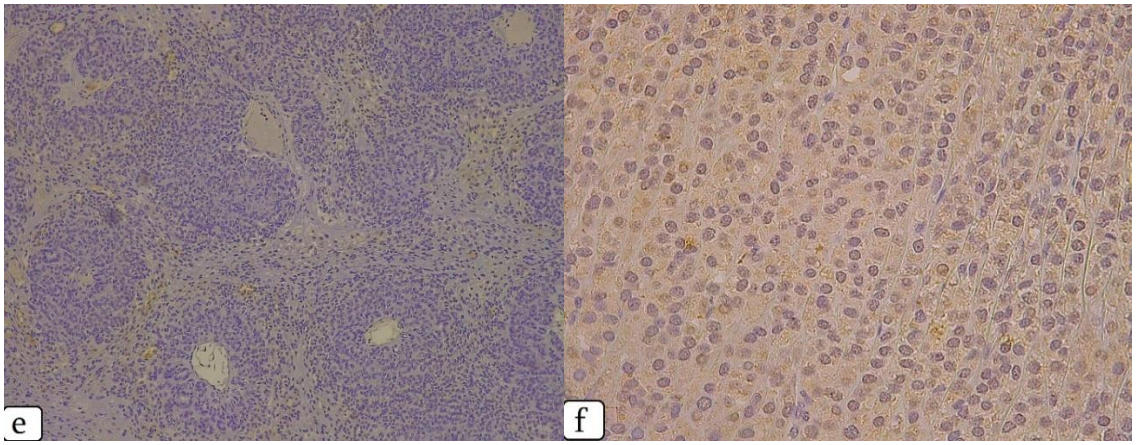


Figure 5. The negative immunohistochemical results for SVPTC case. a – Calcitonin. b – Chromogranin A. c – S100 protein. d – CD56 positive in nonneoplastic and negative for neoplastic area. e – Solid nest pattern negative for HBME-1. f – CEA negative immunoreactivity for tumor cells. Immunoperoxidase reaction. a, c, f - X400; b, d - X200; e – X100.

Outcome and Follow-up

Postoperative radioiodine therapy and thyroid-stimulating hormone suppressive therapy were performed. During the follow-up period, the serum levels of thyroglobulin and anti-Tg Ab were routinely checked. Two months after the surgery patient was referred for a whole-body radioiodine scan and 48 h image after 2 mCi of radioiodine uptake. The child was treated with a dose of 80 mCi for remnant ablation and the post-therapy scan showed no additional iodine avoid lesions.Diagnostic I-131 scintigraphy (whole body) 2 months after surgery: Further diagnosis of iodotherapy. Reveals physiological involvement of the I-131 in the projection area of the oropharyngeal area, large salivary glands, digestive and urinary systems.In addition to physiological involvement, and a very weak area of I-131 accumulation is reflected centrally around the neck, corresponding to the post-thyroidectomy period (Fig. 6).

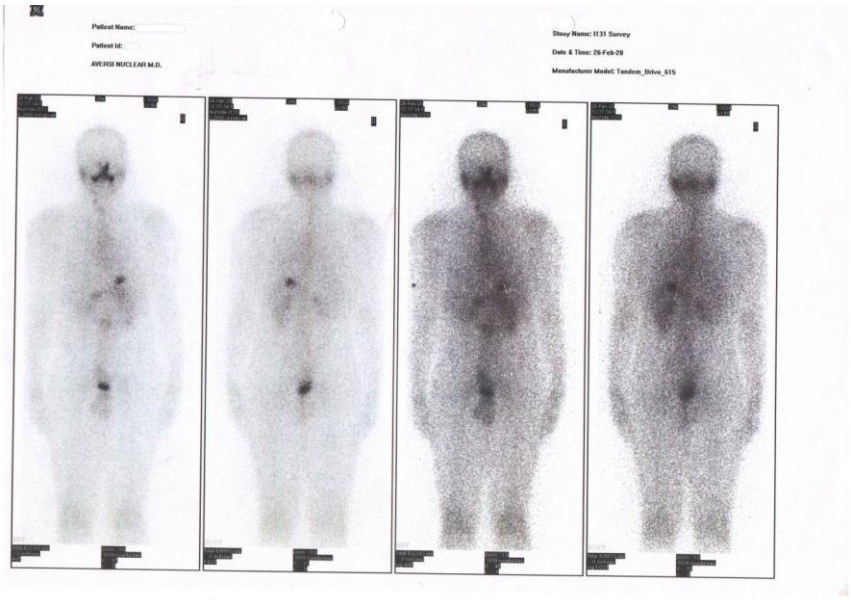


Figure 6. Diagnostic I-131 scintigraphy (whole body) 2 months after surgery 15-old-boy case Laboratory results 6 months after surgery: TSH – 2.25mU/L (0.35 - 4.0 mU/L); FT4 – 1.04 ng/dL (0.89 - 1.76 ng/dL); Thyroglobulin - <0.20 ng/mL (<59.9 ng/dL); Anti-T.G – 11.45IU/mL (0 – 60.0 IU/mL); Vit. D – 27.39 ng/mL (30.0 – 100.0 ng/mL).

Patient is clinically well 12 months after surgery.

DISCUSSION

We present case of 15-year-old boy having solid-trabecular histological type in low-differentiated variant of PTC. The interest in the described case is also determined by the fact that in the preoperative examination of the patient thyroid nodular goiter and Hürthle cell adenoma of indefinite atypia by FNA (Bethesda III) was fixed, no PTC-induced changes and family history and radiation exposure was absent. Intraoperatively unidentified tumor tissue was found; postoperative histological examination showed a PTC solid-trabecular variant of left thyroid lobe. In fact, we had three clinical-morphological versions: 1. Hürthle cell adenoma; 2. Nodular goiter; 3. PTC solid-trabecular variant (Figure 1). Extensive differential-diagnostic research has become necessary with low-differentiated carcinoma, medullary, anaplastic and metastatic tumors for identify both histological subtype as well as its molecular-biological profile. A multicomponent immunohistochemical study was performed, the follow results were obtained: TTF1, Thyroglobulin, E-CAD, Cyclin D1 have shown strong immunopositive reaction. Nuclear protein TTF1, as thyroperoxidase gene translation and thyroglobulin activator [8] shows a total sublimation with a high positive response in papillary carcinoma, in contrast to anaplastic and low-differentiated tumors [9-10]. In our case, E-CAD expression during PTC was preserved. It is noteworthy that, Batistatou et al, (2008) did not report a decrease in E-CAD expression during PTC [11]. It can be assumed, that E-CAD activity varies significantly between different subtypes of PTC, which can be a reason of high expression of the adhesive marker in certain aggressive forms, while in the clinically benign current case - sharply reduced, which is a similar view of other researchers [12]. The unequivocally high expression of Cyclin D1, presented in our case, indicates the activity of phosphorylation, transcription, and translation processes, including S phase and cell cycle progression. We can suggest that the increase in TTF1 translational activity is related to the synchronous reaction of Cyclin D1 and the coordinated activity of these two factors is manifested by tumor tissue growth and differentiation. This phenomenon explains the tumor spread isolated characters and no local metastasis, which is one of highlight of our case.The cytokeratin cocktail AE1/AE3 was also included in the differential-diagnostic panel, which showed weak (+) expression with ≈31–60% cell involvement. Use of this cocktail is limited if the aim of the study is not to confirm epithelial differentiation in the diagnostic panel. The low and high molecular weight clones so-called "pancytokeratin" involvement were excluded, which is critically important in the differential-diagnostic situation, although a low or negative reaction is still not enough to rule out the possibility of carcinoma.Low (3%) expression of Ki-67 is in full correlation with the above characteristics of the cell cycle (Figure 2 f). In our case, a negative reaction of the mesothelium marker HBME-1 was observed (Figure 4 e), thus limiting its use in aggressive forms of thyroid carcinoma.

CONCLUSIONS

The solid-trabecular variant of PTC is relatively rare. Considering all the above-mentioned, differential diagnosis between medullary and anaplastic carcinomas should to be made by using of histological and immunohistochemical methods. Obviously, the high activity of TTF1, Cyclin D1 and thyroglobulin in combination with the activity of E-CAD indicates that in the solid-trabecular variants of PTC, the epithelial phenotype and the transcription activity of thyroid-specific proteins were preserved, which is significant. Therefore, the presented case does not have any features of undifferentiated carcinoma.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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