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Recurrent Thyroid Nodule: Spindle Epithelial Tumor with Thymus-like Differentiation (SETTLE)

ASHU RASTOGI, UMA NAHAR SAIKIA, ASHOK KUMAR GUPTA* AND ANIL BHANSALI

*From the Departments of Endocrinology and *Otolaryngology, PGIMER, Chandigarh, India.*

Correspondence to: Dr Anil Bhansali, Professor and Head, Department of Endocrinology, PGIMER, Chandigarh 160 012, India. anilbhansali_endocrine @rediffmail.com

Received: June 21, 2011; Initial review: July 20, 2011; Accepted: September 5, 2011.

Thyroid nodules are uncommon in childhood and recurrent thyroid nodules even rarer. Spindle epithelial tumor with thymus-like differentiation (SETTLE), a rare and distinctive low-grade neoplasm is amongst the differential diagnosis of solitary thyroid nodule in children. We describe a boy who underwent completion thyroidectomy for SETTLE in the thyroid remnant four years after initial lobectomy was performed for the same diagnosis. Patients with SETTLE are to be closely followed as multifocality may manifest and be detected later.

Key words: *Cytokeratin, Spindle epithelial tumor with thymus-like differentiation (SETTLE), Thyroid.*

Thyroid nodules are uncommon in childhood particularly in iodine sufficient regions and recurrent nodules are even rarer. The prevalence of palpable thyroid nodules in childhood is about 1.5%. The differential diagnosis of solitary thyroid nodule in children are colloid nodule/ adenoma, thyroid cyst, lymphocytic thyroiditis, differentiated thyroid malignancy, medullary thyroid carcinoma and rarely spindle epithelial tumor with thymus-like differentiation [1]. Thyroid nodules are more often malignant in childhood than in adulthood [2].

Spindle epithelial tumor with thymus-like differentiation (SETTLE) is a rare and distinctive low-grade neoplasm of children and adolescents which usually presents as asymptomatic mass or nodule in the neck. Previously it has been described as thyroid spindle cell tumor with mucinous cysts, malignant teratoma and thymoma of the thyroid gland [3]. SETTLE is a tumor derived from ectopic thymus or branchial pouch remnants and was formally characterized as SETTLE by Chan and Rosai [4]. Histopathology and immuno-histochemistry are the gold standard for confirming the diagnosis. There have been less than 30 reported cases of SETTLE in the available literature, and none of a multicentric/recurrent SETTLE [5,6]. We report a case of multicentric SETTLE in either of the lobes of thyroid in a young child.

CASE REPORT

A 9-year-old boy presented with progressively increasing swelling along right side of the neck for 6 months. He had

no history of hoarseness of voice, difficulty in deglutition or breathing, cold intolerance, constipation or symptoms suggestive of hyperthyroidism. He had no history of exposure to radiation and no family history of autoimmune thyroid disease or thyroid malignancy. Ultrasonography detected a hypoechoic mass in right lobe of thyroid and aspiration cytology suggested SETTLE. He was subjected to lobectomy and histopathology confirmed the diagnosis of SETTLE.

During follow up, at the age of 13 years he was detected to have nodular swelling in left lower part of the neck. General and systemic examination was essentially normal except for a scar mark of previous surgery above the suprasternal notch in the midline. Tanner's sexual maturity staging was G2, P2. He had a 3×2 cm firm swelling in the left lobe of thyroid, moving with deglutition, however right lobe could not be palpated. On investigations, his hematological parameters were within normal limits. Biochemical investigations revealed albumin adjusted calcium 9.1 mg/dL, phosphate 4.3 mg/dL, alkaline phosphatase 188 IU/mL. Hormonal investigations revealed T4 7.8 µg/dL, T3 1.7 ng/dL (0.8-1.8 ng/dL), TSH 1.91 µIU/mL (0.5-4.5 µIU/mL), anti thyroid peroxidase 15 IU/mL (<35IU/mL) and calcitonin 5.7pg/mL (<18.2 pg/mL).

Ultrasonography showed 3×2 cm hypoechoic, homogenous lesion in the left lobe of the thyroid. CT scan confirmed the same mass, with extensions into tracheo-esophageal groove and loss of fat planes with esophagus posteriorly, without any evidence of calcification or necrosis. Suspecting a malignant tumor of thyroid PET-CT was done which revealed mild FDG uptake in ill-defined nodule in left lobe of thyroid.

Fine needle aspiration cytology (FNAC) showed cellular smears composed of spindle shaped cells with oval, elongated nucleus suggestive of spindle cell tumor of thyroid. The patient underwent total thyroidectomy. The thyroid specimen weighed 13 g, containing left lobe of thyroid with mass in left upper pole. On cut surface a relatively circumscribed tumor was identified. Microscopically, the tumor cells were arranged in form of vague nodules separated by fibrous septa. Tumor cells were arranged in short interlacing fascicles with oval to spindle shaped and elongated vesicular nuclei. A mitotic count of 6-7/10 high power fields was observed. Immunohistochemistry showed diffuse positivity for cytokeratin, vimentin and smooth muscle actin. Calcitonin and CD68 staining were negative ruling out medullary carcinoma and histiocytic lesions of thyroid and overall features suggesting a diagnosis of SETTLE. The patient received replacement doses of levothyroxine after total thyroidectomy and is disease free for last 2 years.

DISCUSSION

Spindle epithelial tumor with thymus-like elements is an extremely rare tumor of the thyroid, characterized by the proliferation of spindle cells with both epithelial and stromal characteristics. The most common presentation of SETTLE is a nodular thyroid swelling in childhood or adolescence [7]. The age at presentation of patients with SETTLE range from 4 to 59 years, but the tumor occurs predominantly in children, adolescents, and young adults [8]. Clinically, the neoplasm usually manifests as a firm mass involving one lobe of the thyroid for a variable duration. Less commonly, the entire gland is enlarged with hard consistency, and without palpable nodules, mimicking thyroiditis [6]. The present case also presented with unilateral hard swelling. Clinically, the possibilities of nodular goiter, differentiated thyroid malignancy, medullary carcinoma of thyroid and spindle cell tumors of thyroid were considered.

Ultrasound of the neck usually shows a clearly demarcated, solid nodule, except for a few cases in which no nodularity is found and a diffusely hypoechoic structure typical for autoimmune thyroditis is detected [9]. Tumors appear cold scintigraphically and display heterogeneous solid and cystic densities on CT scan. Due to absence of specific clinical symptoms, radiologic findings, or serum markers, a diagnosis of SETTLE is almost always made after histopathologic evaluation as also in the present case.

Certain histological features, including incomplete lobulation, perivascular spaces, biphasic epithelioid/epithelial and spindle cell populations, cysts and cleft-like spaces, and rare, thin epithelial ribbons suggest thymic differentiation. In addition to morphology, immunohistochemistry is important for making the diagnosis of SETTLE. The tumor is typically positive for cytokeratin, vimentin, S-100, smooth muscle actin, and muscle-specific actin and negative staining for EMA, CEA,CK19, calcitonin, thyroglobulin and chromoganin A [6,10]. We also observed positivity for these primary antibodies, hence confirming the diagnosis of SETTLE.

Although SETTLE is considered a tumor with low grade malignant potential, aggressive behavior has been reported in some cases [7]. The neoplasm grows slowly and may cause lymph node and pulmonary metastases many years after diagnosis. Erickson noted that 35% of all reported cases of SETTLE had one metastasis during their course, whereas Cheuk noted a significant metastatic rate of 71% [7,10]. Metastatic disease has also

been described up to 22 and 25 years after the initial operative intervention. Despite the occurrence of metastasis, long-term survival is observed after thyroidectomy. The index patient had a recurrence in other lobe of the thyroid after 4 years of initial presentation and now is disease free for last 2 years.

Formal treatment algorithms have not been established for SETTLE because of the rarity of this tumor; partial thyroidectomy is the current standard of care. However the index case underwent completion thyroidectomy for SETTLE in the thyroid remnant four years after initial lobectomy performed for the same diagnosis. Patients with SETTLE are to be closely followed as multifocality may manifest and be detected later.

Contributors: AR involved in patient care and writing the manuscript. UNS reviewed histopathology. AKG performed the surgery. AB involved in patient care and editing the manuscript. *Funding:* None; *Competing interests:* None stated.

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Biliary Atresia and Cytomegalovirus and Response to Valganciclovir

IRA SHAH AND SUSHMITA BHATNAGAR

From Department of Pediatric Hepatobiliary Clinic, BJ Wadia Hospital for Children, Parel, Mumbai, Maharashtra, India.

Correspondence to:
Dr Ira Shah, 240 D, Walkeshwar Road, Malabar Hill, Mumbai 400 006, Maharashtra, India.
irashah@pediatriconcall.com
Received: July 06, 2011;
Initial review: July 26, 2011;
Accepted: August 06, 2011.

Biliary atresia has been commonly reported with cytomegalovirus (CMV) infection. CMV positive patients may present with a later onset however long term outcome is similar to non-CMV patients. There are very few case reports of role of antivirals in CMV and biliary atresia. We treated a 2 month old girl with biliary atresia who underwent portoduodenostomy at 2½ months of age but continued to have jaundice (bilirubin = 23.6 mg/dl) even after 1 month of Kasai's surgery and subsequently was treated with valganciclovir for 6 weeks following which her jaundice resolved.

Key words: *Biliary atresia, Cytomegalovirus, India, Valganciclovir.*

The pathogenesis of biliary atresia is poorly understood. Association with congenital anomalies in some infants suggests genetic factors. Infection with cytomegalovirus (CMV), group C rotavirus and reovirus type 3 has been associated in certain cases and Fischler, *et al*. found ongoing CMV infection in 39% of patients with biliary atresia [1-3]. CMV positive patients may present with a later onset; however, long term outcome is similar to non-CMV patients [2]. Outcome may also depend on other factors such as age of surgery, bile duct size and presence of liver damage [4]. Though CMV is known to cause neonatal cholestasis, use of antiviral drugs such as ganciclovir and its oral prodrug valganciclovir in patients