

## An unusual manifestation: Papillary thyroid carcinoma in a patient with ataxia-telangiectasia

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Ataxia-telangiectasia (A-T) is a rare autosomal recessive, multisystem, neurodegenerative disorder, characterized by oculocutaneous telangiectasias, variable immunodeficiency and progressive neurological impairment. Definitive diagnosis is made by revealing a disease causing mutation on ATM gene. Missense mutations and polymorphisms of ATM gene can play a role in the development of thyroid papillary carcinoma.

A 13-year-old Turkish girl was diagnosed with ataxia telangiectasia at the age of 8 years. When she was 12 years old, multi-nodular goiter was detected by physical examination and ultrasonography. She underwent thyroidectomy and histopathologic investigation revealed a papillary carcinoma with follicular variant. The patient received post-operative radioiodine therapy as well as L-thyroxine treatment because she had residual lesions. Up until now, she is the first Turkish child with A-T and thyroid carcinoma described in the literature.

*Key words:* ataxia telangiectasia, papillary thyroid carcinoma.

Ataxia-telangiectasia (A-T) is a rare autosomal recessive, multisystem, neurodegenerative genetic disorder. It is characterized by oculocutaneous telangiectasias, variable immunodeficiency and progressive neurological abnormalities such as uncoordinated, ataxic movements as a result of cerebellar cortical degeneration<sup>1-2</sup>. Other features include retardation of somatic growth, premature aging, radiosensitivity and predisposition to cancer<sup>2</sup>. Definitive diagnosis is made by revealing a disease causing mutation on ATM gene which was identified in 1995 in 11q22-23, coding for a protein implicated in genomic homeostasis in case of radio-induced DNA double-strand breaks<sup>1-3</sup>.

Mutations in ATM gene predispose patients to cancer. The cancer incidence for homozygotes is 100-fold greater than that of the general population<sup>4</sup>. Although the exact mechanisms of malignant transformation in A-T patients is not known, loss of cell cycle control, a defect

in DNA repair, or sensitivity to radiation may be responsible<sup>4</sup>. Lymphoid malignancies of both B cell and T cell origin, including non-Hodgkin and Hodgkin lymphoma and several forms of leukemia are reported in A-T patients.

Thyroid papillary carcinoma is the most common carcinoma of thyroid gland, but thyroid carcinomas are rare in childhood. Missense mutations and polymorphisms of ATM gene can play a role in the development thyroid papillary carcinoma<sup>5-9</sup>. Both DNA double-strand break repair pathway and thyroid morphogenesis pathway or dysregulation of thyroid differentiated state maintenance are involved in the etiology of papillary thyroid carcinoma<sup>10</sup>.

We report a 13-year-old girl with ataxia telangiectasia, who developed thyroid papillary carcinoma during follow-up. To our knowledge, she is the first Turkish A-T child with thyroid carcinoma described in the literature.

## Case Report

A 13-year-old Turkish girl, was first referred to our department because of ataxic movements, ocular telangiectasia and recurrent sinopulmonary infections when she was 8 years old. She was born to unrelated healthy parents at 40th gestational week. Her physical examination showed ocular telangiectasia, strabismus, ataxia, dysarthria, dysmetria, nystagmus and positive Romberg test. She had hypogammaglobulinemia; IgG:512 mg/dl (840-1240 mg/dl), IgA:< 5 mg/dl (68-150 mg/dl), IgM: 155 mg/dl (55-140 mg/dl) high alpha-feto protein; 169,3 ng/dl (0-14 ng/ml) levels and inverted CD4/CD8 ratio. Cranial MRI showed cerebellar hemisphere and vermis hypoplasia. She was diagnosed with ataxia telangiectasia and genetic analysis revealed an *ATM* gene mutation (3' UTR. +548 G>T heterozygous, +551 T>C heterozygous). She was treated with regular intravenous immunoglobuline (IVIG) replacement therapy and antibiotics prophylaxis. During follow-up, she had experienced lower respiratory tract infections requiring parenteral antibiotic therapy once or twice a year. When she was 10 years, she developed ulcerated plaques on her right hand second metacarpophalangeal joint. Skin biopsy showed granulomatous lesion with caseification necrosis with negative acid-fast stain. She had antituberculosis treatment and local corticosteroids, with unremarkable response.

At the age of 12 years, multiple thyroid nodules were observed by routine physical examination. The biggest one was painless with 2 cm in diameter on the right lobe of thyroid gland. Thyroid ultrasonography revealed a 26x18 mm solid nodule on the right thyroid lobe, and multiple nodules on both lobes. There was no cervical lymphadenopathy. Thyroid scintigraphy showed multi-nodular goiter with multiple hypoactive nodules on both lobes. The family history for thyroid abnormalities or cancer was negative, and there was no history of previous neither cervical nor chest irradiation. Laboratory investigations showed normal thyroid function tests (TSH: 1.66 mU/ml, free T4: 0,97 ng/dl) and negative autoimmune markers (Anti-TPO: 35 IU/ml, Anti-TG:<20 IU/ml). Thorax magnetic resonance imaging (MRI) and abdominal MRI were negative for metastatic

lesions. Computerized tomography was not preferred for metastatic imaging because of radiosensitivity. The patient underwent total thyroidectomy. Histopathological examination revealed a papillary carcinoma with follicular variant, with no vascular invasion but minimal capsular invasion (Fig.1). Immunohistochemical staining showed positive immunoreactivity for cyclin D1 and cytokeratin 19, and was negative for galectin-3. Thyroid Tc-99m pertechnetate scintigraphy showed residual thyroid tissue after the surgery. Postoperative Anti-Tg levels were also <20IU/ml. L-thyroxine treatment was started and the patient received post-operative radioiodine therapy.

## Discussion

Ataxia-telangiectasia is an autosomal recessive rare multisystem neurodegenerative disorder characterized by oculocutaneous telangiectasias, immunodeficiency and progressive neurological abnormalities. Radiation-induced chromosomal breakage is a hallmark of A-T<sup>11,12</sup>. The incidence of A-T is approximately 1 in 100,000 live births. A-T is caused by biallelic mutations in the *ATM* gene, located on chromosome 11q22.3-23.1. Since the localization of the *ATM* gene to chromosome 11, over 500 different *ATM* mutations have been identified. The *ATM* gene encodes for the protein kinase ATM, a key player in the cellular response to double-stranded DNA damage and multiple cell cycle checkpoint pathways. Malignancy risk is approximately 100 times greater than in the general population<sup>4</sup>. Studies pointed to a high incidence of lymphoid malignancies In patients with A-T, most notably T-cell acute lymphoblastic leukemias. B-cell non-Hodgkin lymphoma and Hodgkin lymphoma were also reported to be frequent<sup>13,14</sup>. In A-T patients, death is usually because of pulmonary infections or malignancies.

Thyroid carcinomas are very rare in childhood, consisting of approximately 0.5% to 3% of all pediatric malignancies and the incidence increases after 10 year of age with a predominance in females<sup>15,16</sup>. Thyroid nodules in pediatric patients are four times more likely to be malignant than in adult patients. Papillary thyroid carcinoma is the predominant type of thyroid cancer. Although pathophysiology of differentiated thyroid carcinoma is not well

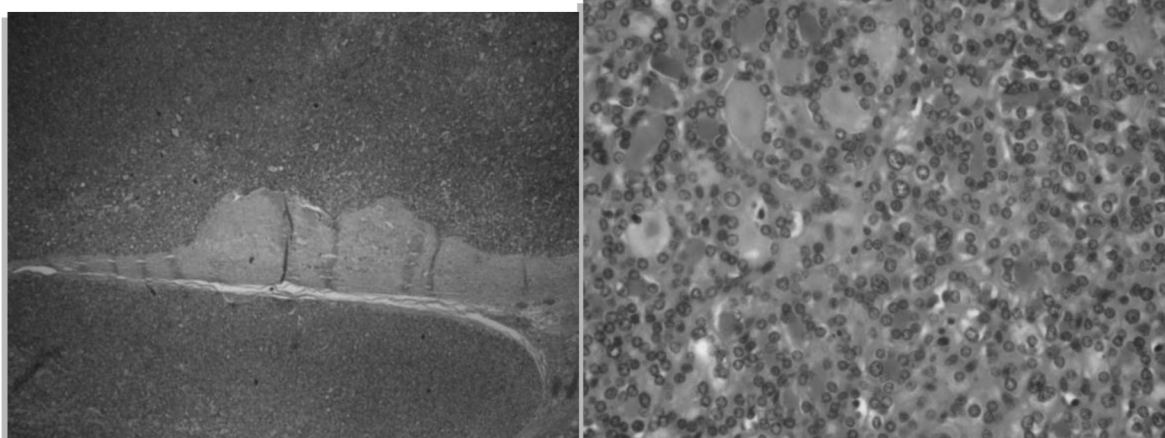


Fig. 1. A) Capsule invasion in minimal invasive carcinoma B) Classical nucleolar characteristics in papillary thyroid carcinoma

defined, exposure to ionizing radiation is known to be a risk factor. Ionizing radiation causes a variation of DNA damages. A-T cells are characterized by an extreme sensitivity of DNA to radiomimetic agents because of alteration of cell-cycle inhibition in response to radiation exposure. *ATM* gene polymorphisms can be a risk factor for thyroid carcinomas (8). First relatives of A-T patients can also develop solid tumors such as breast carcinomas.

Patient reported here is the first Turkish child who developed papillary thyroid carcinoma with A-T. There is only one other A-T child reported by Brasseur *et al*<sup>3</sup>; that was a 9-year-old girl with papillary carcinoma. Suarez *et al.*<sup>13</sup> identified 279 patients with A-T and revealed 69 patients with cancer. Sixty-one of whom were hematologic malignancies. Only one of their patients had thyroid carcinoma. Sandoval *et al.*<sup>14</sup> reported two A-T patients one with follicular thyroid carcinoma, the other with papillary thyroid carcinoma. Even if malignancy risk is greater than normal population in A-T patients, solid tumors are rare than hematologic malignancies. Unfortunately, subsequent risk of developing another malignancy, especially with hematologic origin, is higher in patients with solid tumors. Hecht *et al.*<sup>17</sup> reported that approximately 25% of A-T patients with solid tumors subsequently developed non-Hodgkin lymphoma or leukemia, whereas a very low risk of subsequent neoplasms existed when the first tumor was lymphoid in origin. As the patient had solid tumor at first, she is being periodically screened for neoplasias closely.

In the treatment of thyroid cancers, the best option is the complete surgical resection of the thyroid gland with central lymph node dissection followed by radioactive iodine treatment. Our patient underwent total thyroidectomy. There was no vascular invasion. Because Thyroid Tc-99m pertechnetate scintigram showed residual throid tissue after the surgery, she received radioactive iodine treatment. After 6 months, she is euthyroid and well.

In conclusion, children with ataxia-telangiectasia can develop solid tumors as well as hematologic malignancies. During follow-up, physicians must be alert for thyroid nodules as well as the other malignancies. Early treatment will affect mortality and morbidity.

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