# Cowden syndrome with bronchial asthma

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**SUMMARY: Özsürekci Y, Yavuz ST, Alanay Y, Ütine GE, Kalaycı Ö. Cowden syndrome with bronchial asthma. Turk J Pediatr 2010; 52: 330-332.**

**Cowden's syndrome (CS) is a rare autosomal dominant disorder characterized by multiple hamartomas and an increased risk of breast, thyroid and endometrial carcinomas. Mutations of tumor suppressor gene *PTEN* (phosphatase and tensin homolog) on chromosome 10p23.2, which encodes a lipid phosphatase mediating cell cycle arrest and apoptosis, were first described in CS. Some studies have also implicated *PTEN* in the pathogenesis of bronchial asthma. Herein, we describe a boy with CS referred to the pediatric allergy unit with bronchial asthma symptoms. This patient is one of the very few reported cases with CS with lung disease and possibly the first with bronchial asthma.**

***Key words: Cowden syndrome, macrocephaly, nasal polyps, rectal polyps, lipomas, bronchial asthma.***

Cowden's syndrome (CS) was first described in 1963 by Lloyd and Dennis[1], who named the syndrome after their patient Rachel Cowden. It is a rare autosomal dominant disorder characterized by multiple hamartomas and an increased risk of breast, thyroid and endometrial carcinomas. Germline mutations in the tumor suppressor gene *PTEN* (phosphatase and tensin homolog) on chromosome 10p23.2, which encodes a lipid phosphatase mediating cell cycle arrest and apoptosis, were first described in CS. It has therefore been proposed that all such syndromes based on molecular defects be classified as *PTEN* Hamartoma Tumor Syndromes (PHTS)[2].

Herein, we describe a boy with CS referred to the pediatric allergy unit with bronchial asthma symptoms. This patient is one of the very few reported cases with CS with lung disease and possibly the first with bronchial asthma.

## Case Report

An eight-year-old boy presented with the complaint of wheezing and recurrent cough. The patient was the fourth child of a nonconsanguineous couple. He was born at term following normal delivery. Macrocephaly was noted on antenatal ultrasonography. Birth weight was 4650 g (>97th centile), height was 51 cm (50-75$^{th}$ centile) and head circumference was 46 cm (>97th centile). After delivery, detailed investigations for intrauterine infections and metabolic and endocrine disorders were applied to detect the etiology of macrocephaly. Developmental milestones were normal other than mild delay in head control (6 months). He had frequent upper respiratory tract infections beginning in infancy. At age two, multiple cutaneous masses were noted particularly on the axillary and scapular areas. Rectal and nasal polyps were detected and surgically removed at age three. He was repeatedly hospitalized due to bronchiolitis and was finally diagnosed as asthma and rhinitis at four years of age. Inhaled corticosteroids and bronchodilators were prescribed. There was no family history of allergic diseases.

On physical examination at eight years of age, his height was 124 cm (50$^{th}$ centile), weight 22 kg (25-50p) and occipitofrontal circumference (OFC) was 52 cm (>+2 SD). He had multiple lipomatous soft tissue masses on his neck and right axillary area, approximately 5 cm in diameter. There were no hyperpigmented macules on the penile area. He had mild mental retardation with poor performance at school, and dysmetria and dysdiadochokinesia on neurological examination (Figs. 1a, 1b).

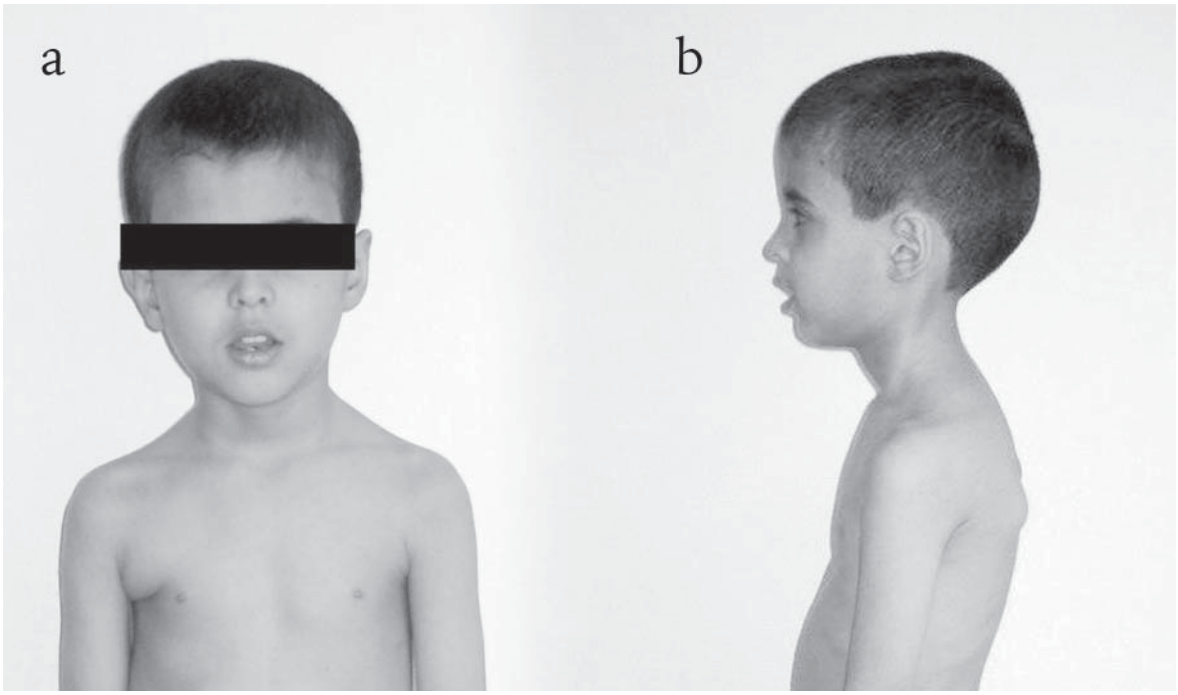


**Fig 1. a-b.** Photographs of the patient: Note the macrocephaly and the lipomatous mass in the right axillary area.

Laboratory tests including complete blood count and kidney and liver function tests were within normal limits. Skin prick tests were positive for cat and house dust mites. Magnetic resonance imaging of the brain did not reveal any cerebellar mass. International Cowden Syndrome Consortium Operational Criteria were applied, and he was diagnosed as CS with presence of one major (macrocephaly) and three minor criteria (gastrointestinal polyps, lipomata and mental retardation)[3].

## Discussion

Cowden syndrome is a rare autosomal dominant condition characterized by multiple hamartomas and neoplasms of ectodermal, mesodermal and endodermal origin. The majority of the existing data on frequencies of clinical features have been obtained from compilations of case reports in the literature, many of which predate the establishment of the 1996 consensus diagnostic criteria[4]. The diagnostic criteria for CS are based on the presence of a pathognomonic mucocutaneous lesion. Hamartomatous overgrowth of tissues derived from all three embryonic origins leads to increased risks for thyroid, breast and possibly other cancers in individuals affected with CS[5]. Therefore, diagnosing the disease is essential for early detection of probable malignancies.

Our patient presented with a history of bronchial asthma, macrocephaly, and lipomatous lesions on the cervical and axillary areas, in addition to a history of rectal and nasal polyps and mild mental retardation. CS and Bannayan-Riley-Ruvalcaba syndrome (BRRS) are the most commonly reported conditions caused by mutations in the *PTEN* gene. They have many overlapping features[6]. Initially thought to be a separate disease, BRRS was subsequently shown to be allelic to CS. In addition, coding sequence mutations in *PTEN* were detected in approximately 60% of patients[7]. However, there are no consensus diagnostic criteria for BRRS, and the diagnosis is usually made by the presence of cardinal features such as macrocephaly, hamartomatous intestinal polyps, lipomatosis, hemangiomas, and pigmented penile macules[8,9]. Our patient presented with the similar symptoms without penile macules; therefore, BRRS was not considered.

Abnormalities of the respiratory tract in CS include laryngeal polyps, cyst of the lung, low-

grade adenocarcinoma of the lung, coin lesions (possibly hamartomas), and arteriovenous malformations[10]. There are also published cases with CS presenting with mesenchymal cystic hamartoma and pulmonary sclerosing hemangioma[11,12].

Our case differs from previously published cases by the presence of concomitant asthma. Even though the association of bronchial asthma and CS has not been reported, some studies have implicated *PTEN* in the molecular pathogenesis of bronchial asthma[13]. Eosinophils are the major effector cells in asthma. Many inflammatory mediators attract and activate eosinophils via signal transduction pathways involving the enzyme phosphoinositide 3-kinase (PI3K)[13,14]. Allergen-induced airway inflammation leads to increased activity of PI3K in lung tissue. A *PTEN* function has been implicated in regulating the PI3K/Akt signaling pathway, at least in part through the regulation of interleukin (IL)-17 expression[15,16].

In addition to this possible link through pathogenesis, the joint occurrence of CS and bronchial asthma in this patient may provide the first clinical evidence for this association.

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