**Paraneoplastic Cushing Syndrome Due To Wilm's Tumor**

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**ABSTRACT**

Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to neoplasm. Paraneoplastic syndromes may be the first or the most prominent manifestations of cancer. Wilm's tumor is the most frequent pediatric renal malignancy and usually presents with abdominal mass. Unusual presentations like acquired von Willebrand disease, sudden death due to pulmonary embolism and Cushing syndrome have been described in the literature. Cushing syndrome, as the presenting symptom of a malignant renal tumor in children, is a very rare entity. Few case reports are available in the literature exploring the option of preoperative chemotherapy as well as upfront nephrectomy. We report a rare case of paraneoplastic Cushing syndrome due to a Wilm's tumor. Based on gradual decrease of postoperative weight, blood pressure, serum adrenocorticotropic hormone, and plasma cortisol levels, along with histological confirmation of Wilm's tumor, paraneoplastic Cushing syndrome due to Wilm's tumor was confirmed.

**Key Words:** Paraneoplastic syndrome.  Wilm's tumor. Cushing syndrome.

**INTRODUCTION**

Paraneoplastic syndromes are collection of symptoms resulting from substances produced by the tumor, at site distant from tumor.1,2 Wilm’s tumor or nephroblastoma is the most common pediatric renal tumor accounting for 85% of all renal tumors.3 ACTH dependent Cushing syndrome, caused by ectopic adrenocorticotropic hormone (ACTH) and/or corticotropin releasing hormone (CRH) production also called paraneoplastic Cushing syndrome, was reported first time in children in 1974.4 Since then only few case reports are available.

We, hereby, present case of a young boy presenting with features of Cushing syndrome and right renal mass, histologically proven as Wilm’s tumor.

**CASE REPORT**

A 2.4-year boy presented to the Outpatient Clinic of Hematology/Oncology Department at The Children’s Hospital and ICH, Lahore, in January 2014 with 1-month history of increased appetite, weight gain, and excessive growth of facial hair. He was normal at birth, vaccinated according to EPI schedule, and a developmentally normal child with no significant past history. His weight was 14 kgs (50th centile), and height was 88 cm (90th centile). He was afebrile with blood pressure of 140/110 mmHg, and pulse rate of 100/minute. He was looking cushingoid and plethoric with hirsutism (Figure 1A). There was no pallor or lymphadenopathy, abdominal striae, petechiae or bruise. Genitalia were normal. His abdomen was distended with a left lumbar mass palpable 5 by 6 cm, that was firm and non-tender.

Baseline laboratory investigations showed hemoglobin= 12 gm/dl, TLC=15.5 K/microliter (53% neutrophils), platelets=251,000, serum sodium=142 mmol/l, potassium=4 mmol/l, blood glucose random=85 mg/dl, serum ACTH=131 (normal < 46.0) serum cortisol level at AM=1540.50 nmol/l (150-660), and PM=584.71 nmol/l (21-195). Dexamethasone suppression test showed no suppression of morning cortisol level and 24-hour urinary vinyl mandelic acid level was normal (6.3 mg/ 24 hours). Ultrasound abdomen showed a 11 x 9 cm mass in right flank inseparable from kidney, suspicion of neuroblastoma/Wilm's tumor. CT scan of chest and abdomen confirmed 12 x 9.5 cm sized heterogeneously enhancing well defined soft tissue density mass arising from the upper pole of right kidney, reaching the midline.

![Figure 1: Child with Cushing syndrome. (A) Pre-treatment. (B) Post-treatment.](image-url)
causing displacement of major vessels to the left (Figure 2). Rt renal vein, IVC and liver had normal appearances. There was no evidence of abdominal lymphadenopathy or ascites. Lungs were normal bilaterally.

Patient was jointly managed by Endocrinologist, and Pediatric Surgeon along with the Pediatric Oncologist. Medical management consisted of control of high blood pressure with antihypertensive (Amlodipine). Hydrocortisone was given in stress dosages pre operatively and subsequently during episodes of fever and vomiting. Right nephrectomy was done.

Histological examination showed round to oval cells with hyperchromatic nuclei and high N/C ratio. Tubule formation, mesenchymal and blastemal element was evident in the submitted biopsy with foci of calcification. Capsule was free of tumor and ureter was not identified. Tumor was positive for WT 1. Morphological features were of Wilm’s tumor.

Postoperative blood pressure normalized and patient was gradually weaned off the antihypertensive. There was rapid decline of ACTH and cortisol level, with postsurgery ACTH level=5.32 pg/ml (normal < 46.0). Final diagnosis was ectopic/paraneoplastic Cushing syndrome due to Wilm’s tumor stage 2 intermediate risk. Glucocorticoid suplementation was done to avoid glucocorticoid withdrawal syndrome. Chemotherapy was started according to SIOP 2001 Wilm’s tumor protocol. Stage 2, intermediate risk chemotherapy consisted of inj. Vinristine 1.5 mg/m², weekly for 8 doses, inj. Actinomycin 45 microgram/kg (9 doses in total), and inj. Doxorubicin 50 mg/kg = starting week 2, 6-weekly. Total duration of chemotherapy was 27 weeks. Patient completed treatment successfully, and Cushingoid features regressed (Figure 1B). He is currently on follow-up and is thriving well.

**DISCUSSION**

A paraneoplastic syndrome is a syndrome that is the consequence of cancer in the body; but that, unlike mass effect, is not due to the local presence of cancer cells. It is due to presence of tumor in the body at a site distant from the tumor or metastasis. The first report of a paraneoplastic syndrome has been attributed to a French physician, M. Auchè, who described peripheral nervous system involvement in cancer patients in 1890, in an adult patient. Since then, only few case reports are available.

The exact pathogenesis is unknown. These phenomena are thought to be mediated by humoral factors (hormones or cytokines) excreted by tumor cells or by an immune response against the tumor. Up to 20% of cancer patients experience paraneoplastic syndromes, but often these syndromes are unrecognized. In children with cancer, paraneoplastic manifestations are even rarer and distinct from those observed in adults. Symptoms may occur in any organ or physiologic system. It may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems. Approximately 5 - 10% of cases of Cushing syndrome (hypercortisolism) are paraneoplastic in etiology.

In Wilm’s tumor, several distinct paraneoplastic syndromes have been reported including hypertension, erythrocytosis, hypercalcemia, Cushing syndrome, and acquired Von Willebrand disease. Till now, only a few case reports are available. Patients with Cushing syndrome, as part of a paraneoplastic syndrome, appear similar to patients with Cushing disease, with the typical moon faces and obesity of the trunk; symptoms caused by human chorionic gonadotropin and urinary gonadotropin peptide are absent; gynecomastia may occur in males.

Because of their protean manifestations, paraneoplastic syndromes should be managed by a coordinated team of physicians, including medical oncologists, surgeons, radiation oncologists, endocrinologists, hematologists, neurologists, and dermatologists. This patient was jointly managed by pediatric oncologist, surgeons and endocrinologist. Surgery and chemotherapy resulted in relatively low cortisol levels because the normal corticotropin cells have been surpassed by hypercortisolism due to ACTH producing Wilm’s tumor. Glucocorticoid suplementation was used to avoid...
glucocorticoid withdrawal syndrome. This supplementation was tampered after the hypothalamic-pituitary-adrenal axis had recovered.9

Knowledge about paraneoplastic manifestations can be of great clinical importance because they may be the presenting sign of a tumor or its recurrence; and hence, facilitate early diagnosis. In contrast, they sometimes mask the symptoms of a tumor and cause diagnostic delay. If an underlying cancer is not found, surveillance should continue for several years.10

REFERENCES