The Gulf Journal of Oncology

ISSUE 12                        JULY 2012

TABLE OF CONTENTS

Original Studies

Penile Cancer in India: A Clinicoepidemiological Study ................................................................. 07
M. Pahwa, M. Girotra, A. Rautela, R. Abrahim

Gastric Cancer: A Retrospective Analysis from AIIMS, New Delhi .................................................. 11
R. Hadi, B.K. Mohanti, S. Pathy, G.K. Rast, N.K. Shukla, S.V.S. Deo, A. Sharma, V. Raina

Review Articles

Intensity Modulated Radiotherapy (IMRT) In Head and Neck Cancers – An Overview ............................. 17
C.M. Nutting

Adult T-Cell Leukemia/Lymphoma ........................................................................................................ 27
K.I. Rasul, Z.A. Barwari

Case Reports

Adrenocortical Tumors in Children: A Kuwait Experience ................................................................. 38
R. Mittal, D. G. Ramadan, N. M. Khalifa, S. O. Khalifa, Z. Mazidi, M. Zaki

Limb Sparing Surgery in Soft Tissue Sarcoma of Extremities: An Indian Perspective ............................ 47
R.V. Bhargavan, P. Kumar, K.C. Kohar

Mixed Germ Cell Tumor of Ovary and Clitoromegaly in Swoyer’s Syndrome: A Case Report .................. 55
S. Aminimoghaddam, B. Mokri, F. Mahmoudzadeh

Palmar Fasciitis and Arthritis Syndrome Associated With Metastatic Ovarian Cancer: A Paraneoplastic Syndrome ........................................................................................................ 59
I.K. Nahar and M. S. Al-Rajhi

Trichilemmal Pilar Tumor of the Scalp: A Case Report .......................................................................... 62
K. Al Saleh, H.S. Hooda, H. El-Wakiel, R. Safwat, A. Bedair, W. Eskaf

Carcinosarcoma of Renal Pelvis with Immunohistochemical Correlation ............................................. 65
S.D. Deshmukh, V.L. Gaopande, D.P. Pande, G.S. Pathak, B.K. Kulkarni

5-Flourouracil Cardiotoxicity – An Elusive Cardiopathy: Case Report ................................................... 70
G. M. Bhat, M. H. Mir, H. I. Showkat, B. Kasanna, F. Bagdadi, A. H. Sarmast, S. Qadri

An Unusual Variant of Prostatic Adenocarcinoma with Metastasis to Testis: A Case Report .................... 73

Mammary Fibromatosis in a Male Breast ................................................................................................ 77
N. Al-Saleh, T. Amir, I. N. Shaf

Primary Isolated Extramedullary Plasmacytoma of Mesentry: A Rare Case Report ................................. 81
R. Ghalhotra, K. Saggar, K. Gupta, P. Singh

Feature Article

Balsam Organization for rehabilitation and support for cancer patients and their families .......................... 85

Conference Highlights / Scientific Contribution

- Conference Highlights – 1st Palliative Care Conference in Kuwait ..................................................... 86
- News Notes ......................................................................................................................................... 89
- Advertisements ................................................................................................................................. 91
- Scientific events in the GCC and the Arab World for the 2nd Semester of 2012 .................................. 92
Adrenocortical Tumors in Children: A Kuwait Experience

R. Mittal¹, D. G. Ramadan², N. M. Khalifa¹, S. O. Khalifa¹, Z. Mazidi², M. Zaki³

¹Unit of Pediatric Oncology, Department of Medical Oncology, Kuwait Cancer Control Centre, Kuwait
²Endocrine Unit, Pediatric Department, Al Sabah Hospital, Kuwait
³Pediatric Department, Farwaniya Hospital, Kuwait

Abstract

Introduction:
Adrenocortical tumors (ACT) are rare tumors of childhood. The majority of these tumors is hormone-producing and cause virilization and Cushing syndrome or feminization.

Methodology:
The authors describe 6 cases of adrenal cortical tumors treated at the Kuwait Cancer Center which were presented over a period of 20 years (1989-2009).

Results:
The mean age was 5.5 years (range 15 months – 12 years). All had signs of virilization. One child had hypertension, while 2 had a metastatic disease at presentation. The diagnosis was made by clinical signs and symptoms, high levels of relevant adrenal hormones and imaging. Two children were not fit for surgery; one was too sick for any treatment and died shortly after diagnosis, while the other died after receiving one cycle of palliative chemotherapy. Four patients underwent complete surgical resection and achieved complete remission, three of whom later had recurrence (distant in one and local in two patients) and succumbed due to progressive disease. Mitotane was used in two children. Only one patient is currently surviving and well nearly 13 years after her surgery. In our series, the long-term outcome of children with adrenocortical tumors was very poor.

Conclusions:
Virilization is an important clue to the diagnosis of ACT. Early diagnosis and complete surgical resection are important for survival. Metastasis at presentation or as recurrence carries very dismal prognosis.

Keywords
Adrenocortical tumor, Adrenal neoplasm, Virilizing adrenal tumor, Pediatric hormone secreting tumors.

Introduction
Adrenocortical tumors in children are extremely rare, accounting only for 0.3-0.4% of all neoplasms in this age (1-2). Increased incidence of this tumor has been reported from southern Brazil (3-4). Most frequently, the tumors secrete hormones resulting in virilization in females, pseudopuberty in males, and cushingoid features. Other symptoms include palpable abdominal mass and hypertension. The number of reported cases is small, and few series have been published from various institutions (5-10). Keeping in view the lack of adequate number of children with this tumor, an international registry called International Pediatric Adrenocortical Tumor Registry (IPACTR) was established at St. Jude’s Hospital, Memphis, USA (11). Kuwait Cancer Control Centre is the only comprehensive cancer hospital in Kuwait. Its pediatric unit registers between 40 – 50 new cases of pediatric solid tumors including lymphomas per year. In the last 20 years, we registered 6 ACT cases. In this article we report the outcome of treatment of these 6 children along with a review of the literature.

Corresponding author: Dr. Rakesh Mittal, Consultant & In-charge, Pediatric Oncology, Department of Medical Oncology, P.O. Box 42262, Shuwaikh 70653, Kuwait. Phone: 965-24849100 – 4532. Fax: 965 – 24810007. Email: rakeshmittal55@hotmail.com
Methodology

This is a retrospective analysis of all the 6 cases which were registered and treated at the Kuwait Cancer Center which were presented over a period of 20 years (1989-2009).

Case Reports

Case No. 1: MZ was 4 years old when she presented with a 6-month history of virilization with clitoromegaly and growth of fine facial and coarse pubic hair. She was not cushinoid. She had normal levels of serum cortisol, ACTH, aldosterone but had elevated levels of adrenal androgens; dehydroepiandrosterone sulphate (DHAS) and testosterone. Ultrasound (US) and CT scan abdomen showed a large left suprarenal mass 7 cm in diameter with calcification, displacing the left kidney. Left adrenalectomy was performed. Pathologic diagnosis was adrenocortical carcinoma. Post-operatively, the levels of adrenal androgens normalized and she was followed up. Five months later, she had re-growth of facial and pubic hair. Levels of adrenal androgens were elevated. CT scan showed recurrence of the tumor infiltrating the left kidney with large para-aortic lymph nodes. She was given mitotane without effect and she died four months later.

Case No. 2: SH was nearly 15 months old when she developed signs of virilization (pubic hairs Tanner stage III). Imaging studies revealed a left adrenal tumor. She had high androgens, aldosterone and high cortisol levels. Other metastatic work up did not reveal any site of distant metastasis. She underwent left adrenalectomy. Her hormone levels became normal after few weeks. She is under regular follow-up without any evidence of recurrence. She is almost 13 years after surgery, healthy and with normal growth parameters.

Case No. 3: YK was 12 years old when she presented with headache, aggressive behavior, focal convulsions and low-grade fever. CT scan, lumbar puncture, electroencephalogram and fundus examination were normal. She was managed with symptomatic drugs but symptoms reappeared after 3 weeks with headache, blurred vision, unsteadiness and focal and generalized convulsions. She was found to be hypertensive. Imaging studies of abdomen by US-/CT-/MRI scan revealed right suprarenal mass (11.2 x 13.5 x 13 cms) with liver metastasis. Chest X-ray showed multiple pulmonary metastases. Bone marrow aspiration-/Biopsy, and the bone scan were normal. MIBG scan was negative. She had high androgens, aldosterone and cortisol levels, the latter were not suppressed by the dexamethasone suppression test. On the basis of the above investigations, a diagnosis of secretory virilizing adrenal tumor with lung and liver metastasis was made. She was planned for palliative chemotherapy, however, her family did not agree for any treatment and she was taken home against medical advice. The family brought her back nearly one month later, by which time her disease had progressed and her general condition had deteriorated. Nevertheless, a trial of chemotherapy with cisplatin and vincristine was initiated, but she died within 3 days of admission.

Case No. 4: MM was 10 years old when he was admitted with a 4 to 6 months history of hypertrichosis, obesity, fever and signs of Cushing syndrome. He also had significant swelling over the lower legs and scrotum. Imaging studies revealed a huge mass arising from the right adrenal gland with pulmonary metastasis. Doppler study showed a large thrombus in the inferior vena cava (IVC) extending up to the right atrium, which explained the oedema of the lower limbs and scrotum. He had enlarged penis and pubic hair Tanner stage 2. His relevant adrenal hormone levels were high. He was not fit for any surgical intervention. The family was offered palliative chemotherapy but they refused. The child died after few days due to progression of his disease.

Case No. 5: KH was 5 years old when he developed signs of virilization (enlarged penis/pubic hairs). On palpation he was found to have a left hypochondrial mass. Imaging studies showed a large left adrenal mass. All the relevant hormone levels were high. He underwent left adrenalectomy and left nephrectomy. Post surgery, the hormones level normalized within one month. He was kept under follow-
up. Unfortunately he developed widespread metastatic disease within 4 months of the surgery and died due to progression of his disease 7 months after the operation.

Case No. 6: KS was 5.5 years old when she presented to the peripheral hospital with cushinoid features and virilization (clitoromegaly and pubic hair Tanner stage IV. Imaging studies revealed a large left suprarenal mass. Her serum cortisol level and adrenal androgens were significantly high. She underwent resection of the tumor with subsequent normalization of her hormone levels. Pathological diagnosis was reported as adrenal cortical carcinoma. She was kept on close follow-up. She had a local recurrence after 6 months with elevated adrenal hormone levels, and underwent a second resection. She was given adjuvant chemotherapy according to St. Jude’s protocol for ACT (Etoposide, Cisplatin, Adriamycin and Mitotane) for 6 months. After completing her chemotherapy, she continued to be in her second remission. She was closely followed up but unfortunately she developed local recurrence of the tumor after 8 months. Surgeons ruled out the possibility of second surgery. She was kept only on supportive care and died after 4 months of local recurrence due to progression of her disease.

**Results**

The epidemiological data are shown in Table 1. The median age at presentation was 5.5 years, though there was a wide variation (15 months to 12 years). The female to male ratio was 2:1. All had virilization as initial symptoms. Cushinoid features were prominent in Cases 4 and 6. Case 3 had a peculiar presentation with CNS symptoms, which were probably due to her uncontrolled hypertension leading to hypertensive encephalopathy. Case 4 had a large thrombus in the IVC, which led to significant lower limb edema. Two patients (Cases 3 and 4) had metastasis at presentation. The specific laboratory data are shown in Table 2.

The treatment and final outcome data is depicted in Table 3. Three children underwent adrenalectomy. Case 3 and 4 had very advanced disease with distant metastasis; hence no surgery was carried out, and both died without any treatment. Of the 4 children who had surgery, 3 developed recurrence. Case 5 developed distant metastasis after successful surgery and died few months after recurrence without any salvage therapy, while Case 6 had local recurrence 6 months after the initial surgery. She had a second surgery and again achieved a CR status. This time she received chemotherapy for 6 months along with mitotaine. Unfortunately, the tumor recurred again locally 8 months after completing the chemotherapy. A third surgery was not possible, and she soon died due to progressive disease. Out of the 6 children, 5 died due to their disease, while one is surviving 13 years after the initial surgery.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Sex</th>
<th>Nationality</th>
<th>Age at Presentation</th>
<th>Virilization</th>
<th>Additional symptoms</th>
<th>Site of primary</th>
<th>Metastasis at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>M</td>
<td>K</td>
<td>4 years</td>
<td>+++</td>
<td>Nil</td>
<td>Lt adrenal</td>
<td>Nil</td>
</tr>
<tr>
<td>2.</td>
<td>F</td>
<td>F</td>
<td>15 months</td>
<td>+++</td>
<td>Nil</td>
<td>Lt adrenal</td>
<td>Nil</td>
</tr>
<tr>
<td>3.</td>
<td>YH</td>
<td>K</td>
<td>12 years</td>
<td>++</td>
<td>Hypertension</td>
<td>Rt adrenal</td>
<td>Liver / Lung</td>
</tr>
<tr>
<td>4.</td>
<td>MM</td>
<td>NK</td>
<td>10 years</td>
<td>++</td>
<td>Fever / Swelling limbs</td>
<td>Rt adrenal</td>
<td>Lungs</td>
</tr>
<tr>
<td>5.</td>
<td>K</td>
<td>M</td>
<td>5 years</td>
<td>+++</td>
<td>Nil</td>
<td>Lt adrenal</td>
<td>Nil</td>
</tr>
<tr>
<td>6.</td>
<td>KS</td>
<td>NK</td>
<td>5.5 years</td>
<td>+++</td>
<td>Nil</td>
<td>Lt adrenal</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Table 1: Epidemiological features

M: Male    F: Female    K: Kuwaiti    NK: Non Kuwaiti
Adrenocortical tumors in children, R. Mittal, et. al.

Table 2: Hormone profile of cases

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testosterone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>12.3</td>
<td>16.36</td>
<td>34.2</td>
<td>50.4</td>
<td>33.77</td>
<td>25.6 l</td>
</tr>
<tr>
<td>Post-operative</td>
<td>0.1</td>
<td>0.32</td>
<td>-</td>
<td>&lt;0.1 → 2.1</td>
<td>-</td>
<td>&lt;0.069</td>
</tr>
<tr>
<td>** Estradiol**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pmol/l</td>
<td>242.23</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DHEAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>umol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>25.7</td>
<td>16.1</td>
<td>19.1</td>
<td>-</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Post-operative</td>
<td>0.13</td>
<td>0.1</td>
<td>0.5 → 17.4</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Cortisol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>304</td>
<td>1420</td>
<td>1253.33</td>
<td>560</td>
<td>885.27</td>
<td>1138</td>
</tr>
<tr>
<td>Post-operative</td>
<td>340</td>
<td>139</td>
<td>-</td>
<td>7 → 499</td>
<td>-</td>
<td>6.52</td>
</tr>
<tr>
<td><strong>17OHP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>Normal</td>
<td>11</td>
<td>-</td>
<td>20.16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-operative</td>
<td>Normal</td>
<td>1.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Aldosterone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>456</td>
<td>2651</td>
<td>-</td>
<td>-</td>
<td>899</td>
<td></td>
</tr>
<tr>
<td>Post-operative</td>
<td>598</td>
<td>701</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Androstenedione</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>-</td>
<td>105</td>
<td>-</td>
<td>&gt;34</td>
<td>&gt;34</td>
<td>19.8</td>
</tr>
<tr>
<td>Post-operative</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 3: Outcome of treatment

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Sex</th>
<th>Surgery</th>
<th>Outcome</th>
<th>Chemotherapy</th>
<th>Recurrence</th>
<th>Final outcome</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F</td>
<td>Left adrenalectomy</td>
<td>CR</td>
<td>Mitotaine</td>
<td>Yes</td>
<td>Died</td>
<td>5 months</td>
</tr>
<tr>
<td>2.</td>
<td>F</td>
<td>Left adrenalectomy</td>
<td>CR</td>
<td>Nil</td>
<td>Nil</td>
<td>Alive</td>
<td>13 years</td>
</tr>
<tr>
<td>3.</td>
<td>F</td>
<td>Nil</td>
<td>-</td>
<td>One cycle</td>
<td>-</td>
<td>Died</td>
<td>Nil</td>
</tr>
<tr>
<td>4.</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>Nil</td>
<td>-</td>
<td>Died</td>
<td>Nil</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
<td>Left adrenalectomy</td>
<td>CR</td>
<td>Nil</td>
<td>Yes</td>
<td>Died</td>
<td>4 months</td>
</tr>
<tr>
<td>6.</td>
<td>F</td>
<td>Left adrenalectomy</td>
<td>CR</td>
<td>adjuvant after recurrence and second surgery</td>
<td>Yes</td>
<td>Died</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Table 2: Hormone profile of cases

Normal pre-pubertal values are as follows;

- Testosterone: M= Tanner 1, age < 9.8y: <0.1-0.35 nmol/L - Tanner 2, age 9.8y to 14 y: 0.62-5.20 nmol/L
- F= Tanner 1, age < 9.8y: <0.1-0.35 nmol/L - Tanner 2, age 9.8y to 14 y: 0.24-0.97 nmol/L
- DHEAS (Dehydroepiandrosterone sulfate) M= 0.34-2.16 umol/L, F 0.49-2.96 umol/L
- Cortisol 8 am reading: 138-635 nmol/l
- Aldosterone: 111-862 pmol/l
- Androstenedione: 1.7-9.4 nmol/l

Discussion

Incidence

Adrenocortical tumors (ACT) are very rare. Their global incidence is around 0.3-0.4 % of all neoplasms in children (1). The reported incidence in US is 0.2 – 0.3 cases per million (2). The incidence of ACT is not uniform all around the world. A 10–15 fold increase in its incidence has been reported from south Brazil (3-4). IPACTR had collected database for nearly 250 children with ACT until 2005 (11-12). Preponderance of females with ACT is a well-established fact in the adult population, but higher incidence of females in children (female: male ratio 1.5:1) has also been reported (12-13). A much higher ratio (female:
male ratio 2.3:1) was reported by Hayles et al (14). Though the numbers are very small in our series, we had 4 females and 2 males (ratio 2:1). The majority of series have reported clustering of cases below the age group of 5 years, but in our series, the median age was 5.5 years with the age range from 15 months to 12 years.

**Genetic markers**

Adrenocortical tumors can be associated with various congenital genetic syndromes like Li–Fraumeni syndrome, Beckwith–Wiedmann syndrome, Carney syndrome, Multiple Endocrine Neoplasia type I (MEN1), and congenital adrenal hyperplasia. Germline TP53 mutation is almost always the predisposing factor in childhood ACT(3, 15). Rebiero et al (3) reported a unique germline mutation (TP53-R337H) from Southern Brazil, where the incidence of ACT is 10-15 times the general incidence. Letronico et al (16) reported germline Arg337His mutation of p53 protein in 77.7% of children with benign or malignant sporadic adrenocortical tumors. It has also been postulated that TP53, IGF2, H19, p57kip2, and MEN1 genes are involved in the carcinogenesis of ACTs along with ACTH–c, AMP–PKA and Wnt pathways (17). A novel germline variant hotspot mutant P53-R175L was identified by West et al (19) in pediatric adrenocortical tumors. Though no consistent genetic marker has been identified, Figuerido et al (18) reported 9q34 amplification by using genomic hybridization technique. West et al (20) reported differences in the gene expression between adrenocortical adenomas and carcinomas. They also reported that pediatric adrenocortical carcinomas share the similar pattern of gene expression as reported for adults with adrenocortical carcinomas. In our series, we did not find any case with genetic congenital abnormality. Due to lack of facilities, no cytogenetic analysis was performed in our series. Family history may be important in some cases (21-23). A strong family history with other malignancies was described by Kenny et al (24).

Adrenocortical tumors in children, R. Mittal; et. al.

Though no known etiological factors have been found, some suggestions have been made that ACTs may be congenital in origin because of its association with the fetal zone of fetal adrenal cortex (25-26). Its association with congenital adrenal hyperplasia has led to the theory that it could be due to chronic ACTH stimulation (27, 28).

**Clinical Presentation**

The median age for the development of ACT mentioned in the literature is around 3.9 – 4 years (7-8). In our series, the median age was 5.5 years. The signs and symptoms of ACTs are related to the tumor size (mass effect), overproduction of androgens lead to pseudopuberty in males and virilization in females. Signs of virilization include rapid growth, hirsutism, acne, increased muscle mass, facial and pubic hair, and penile or clitoral enlargement (6).

Cortisol overproduction can lead to Cushing syndrome in either sex. Hyperestrogenism (feminization) or aldosteronism Conn syndrome can also be seen rarely. More than 90 % of the children have functional tumors, but in older children non-functional tumors are more common. Virilization syndrome is more common in children (7-9), whereas adults have mixed virilization/hypercortisolism syndrome. All our patients had signs of virilization at presentation. Other symptoms include pain in abdomen, which is seen in about 50% of the children. Hypertension due to high aldosterone could be a presenting symptom (7). In our series, one child had malignant hypertension. Adrenocortical adenomas usually present as localized disease while adrenocortical carcinomas may present with metastatic disease. Teinturier et al (8) reported localized disease in 80% of the children, loco regional in 7%, while 13% had metastasis at presentation. However Ciftci et al (9) reported 80% incidence of metastasis in children with ACC. The common sites of metastasis are lung, liver, bone, and kidney. In our series, 2 children had metastasis at presentation.

**Diagnosis**

The diagnosis of the functional ACTs is straightforward in the majority of cases. Presence of a large adrenal mass on imaging studies with laboratory evidence of high adrenocortical hormones in urine or blood can easily clinch the diagnosis. Imaging studies are very important to plan the surgery. CT / MRI scans are important in delineating the extent
of the tumor, and to see distant metastasis. Imaging studies typically demonstrate a large, circumscribed, predominantly solid suprarenal mass with variable heterogeneity due to central necrosis or hemorrhage (3). Calcification is not uncommon (29). The same authors also suggested that finding of increased retroperitoneal fat due to hypercortisolism on the CT scan and MRI images of children with an adrenal mass favors the diagnosis of adrenocortical neoplasm. US abdomen is not a sensitive investigation to pick up the primary lesion (6) but is important to rule out the presence of any vascular invasion, e.g. the presence of thrombus in IVC, which could pose a real threat for pulmonary embolism (29).

In a study of 34 children, US, CT scan and MRI exhibited specificity of 100% in the diagnosis of vascular invasion, with sensitivity of 50%, 66% and 100%, respectively (30). In children, the term adrenocortical neoplasm or tumor is applied because adrenal adenoma and adrenal carcinoma may be difficult to distinguish histopathologically (29).

The common hormones which are tested in urine for the diagnosis of ACTs are the 17-ketosteroids (which are adrenal androgens and metabolites), 17-hydroxycorticosteroids (cortisol metabolite), DHA, and free cortisol (1, 3, 5-7). Serum testosterone is elevated in virtually almost all cases of ACTs with virilization. Other hormones which can be elevated in serum are DHA, DHAS, and cortisol. High estrogen levels can result from peripheral conversion of adrenal androgen or due to direct adrenal hyperproduction. Dexamethasone suppression test is often used to differentiate ACTs from adrenal hyperplasia (1). Rarely these tumors may be suppressible.

**Prognostic features**

In almost all the published data, there is a long list of prognostic factors when analyzed as univariate factors, but on multivariate analysis, only large tumors and presence of metastasis at presentation were considered as poor prognostic features (2, 7). Rodriguez et al (12) reported age, tumor size, and resectability as important prognostic indicators, while Tucci et al (30) reported tumor stage as the most important prognostic factor in multivariate analysis. In a series of 20 children with small ACTs (Volume < 200 cm3 or weight < 100 gm), there were only 18 surviving children after surgery (11, 31). Partial excision and advanced stage disease may be the major determinants of the poor outcome (9). Other histopathologic poor prognostic features reported in literature are invasion of the capsule, venous invasion or invasion of the adjacent organs. Riberio et al (7) reported tumor volume > 200 ml, or weight > 80 gm, and age more than 3.5 years as the worst prognostic features. They also suggested strong association of aggressive behaviour with higher urinary 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OH) secretion. In the analysis of patients registered with IPACTR (11), the most important favorable prognostic factors were age < 3 years, tumor weight less than 200 gms, virilization, and stage I disease. Curative resection, precursor secretion, recent diagnosis, and local stage could be associated with favorable survival (32). Immunohistochemical markers are not predictive of the outcome (33).

**Surgery**

The definitive treatment of ACTs has always been surgical resection of the tumor (1, 6, 10, 29, 35). Radical resection sometimes requires nephrectomy, resection of the liver segment as well as portion of the pancreas. However, even this extensive curative resection does not guarantee a long term survival as more than 50% of the patients will have recurrence either loco – regional or distant or both. In view of high cortisol production and subsequent suppression of contralateral adrenal gland, it is always advisable to start cortisol replacement perioperatively. Lee et al (6) recommended intramuscular depot of cortisone acetate in stress quantities, which should be started 2 days prior to the surgery, and should be tapered over three days postoperatively. They also recommended mineralocorticoid replacement in some patients. Since nearly 20% of the tumors have infiltration of the vena cava by thrombus, it is important to manually palpate the extent of the thrombus. Thrombectomy for inferior vena cava tumor extension has been advocated by various
Adrenocortical tumors in children, R. Mittal, et. al.

authors(30, 36), Borelli et al (37) reported that for recurrent disease, either locally or distant, surgery is still the best approach. In our series four children had primary resection, out of which two had local recurrence, and one had distant metastasis. Only one child is surviving, he is disease free and 13 years after the initial surgery.

Role of chemotherapy

Chemotherapy has very limited role in the treatment of malignant adrenocortical tumors. As mentioned previously, surgery is the only curative treatment. Chemotherapy offers no survival advantage when given in adjuvant setting (8). Chemotherapeutic agents including mitotane (o,p'-DDD) and cisplatin have been used in metastatic setting. Mitotane acts both by inhibiting the biosynthesis of corticoids and the destruction of adrenocortical cells leading to fibrosis. However, it can cause serious gastrointestinal and neurological side effects. Sandrini et al (13) termed it as an experimental drug. Other chemotherapeutic agents, which have been used, are etoposide, 5 FU, carboplatin, and ifosfamide. No firm conclusions can be drawn regarding their effectiveness and the real benefits of chemotherapy are still debatable. In our series, two children received mitotaine but there was no long-term survival benefit. Hah JO (36) reported a single case of metastatic ACC, who was successfully treated with high dose chemotherapy and autologous stem cell transplant.

Role of radiotherapy

Radiation therapy has been used by some authors with doubtful benefits. ACTs are generally considered to be radio-resistant (38). Radiation therapy has been reported to improve local control but with no advantage in disease-free or overall survival (39). However, because of high incidence of TP53 mutation in children with ACC, radiation may increase the incidence of second malignancy in these children. Driver et al (40) reported that 3 out of 5 cases who received radiotherapy developed sarcomas in the radiation field and died subsequently. Role of radiofrequency ablation in the treatment of adrenocotical tumors has also been suggested (41).

Survival

Survival for small resectable tumors is in the range of 80% (9), while for large, unresectable or metastatic tumors, the outcome is dismal. Tucci et al (30) reported overall 5-year survival rates of 100% in stage I, 85% in stage II, 40% in stage III and 0% in stage IV. Michalkiewicz et al (11) reported 5 years event free survival of 54.2% for the group of 254 children less than 20 years. In most of the published case reports, there was no survivor, who had unresectable or metastatic disease. In our series, we had only one long-term survivor out of the 6 children. In the adult population, the reported 1-year survival rate is less than 40% (42) while the reported 5 year disease-free survival is around 30% (43).

Conclusion

ACTs are rare tumors of childhood. They present with signs of virilization or cushinoid features. The long- term survival depends on the extent of resection and presence or absence of metastasis. Chemotherapy and radiotherapy have a minimal role in its management. Multi-institutional and prospective studies are necessary for a complete understanding of the pathogenesis these tumors and to improve the outcome.
References


