Bronchial Carcinoid tumour as a rare cause of Cushing’s syndrome in children – A case report and review of literature

What is already known on this topic?
The incidence of Endogenous Cushing’s syndrome is 0.7-2.4 per million people per year with only 10 percent of cases occur in children and adolescents. Ectopic ACTH syndrome (EAS) accounts for 10 percent of cases of CS in adults but is it is a very rare condition in the paediatric population. Furthermore, the bronchial carcinoid causing Cushing’s syndrome is extremely rare with only a few cases reported in literature and very less is known about its response to the treatment.

What this study adds?
The rarity of disease necessitates the accumulation of data of each case to understand the clinical behaviour and the response achieved by appropriate management and strict follow up. This paper presents the current state of knowledge about Cushing’s syndrome due to bronchial carcinoid in paediatric patients and includes the clinical presentation, pathophysiology, approach to diagnose and treat this rare condition and its clinical outcome. The illustration of imaging, pathological slides and clinical photographs also contributes to better understanding of these aspects of disease.

Abstract
Introduction- Cushing’s syndrome (CS) is rare in childhood and adolescence. The most common cause for CS in children is exogenous administration of glucocorticoids in the form...
of topical, inhaled or oral corticosteroids. Endogenous causes can be classified into adrenocorticotropic hormone (ACTH) independent and ACTH dependent causes.

**Material and methods**-The English literature was searched from 2019 to oldest via PubMed, Google and Google scholar using keywords; "Ectopic ACTH Syndrome in children”, “Bronchial carcinoid in children” and “Cushing’s Syndrome in children. The patients of Bronchial carcinoids causing Ectopic ACTH syndrome (EAS) and reviewed their variables like age, sex, type of carcinoid, investigations, surgery, recurrences and outcome.

**Results**- We found 14 cases of pediatric bronchial carcinoid producing ACTH in literature with mean age of 15.8 years and female preponderance. Most of the patients had right lung lesion and typical carcinoid in histology. We also describe our experience of managing a 12 year old, female, who presented to us with features of Cushing’s syndrome and found to have ectopic ACTH secreting bronchial carcinoid, which was resected surgically.

**Conclusion**- Bronchial carcinoid is extremely rare in children and only 4% of them are associated with CS. The postoperative treatment of CS is challenging with high prevalence of hypertension, increased BMI and visceral fat mass, impaired cognitive functions and decreased quality of life. Our patient was managed successfully by multidisciplinary approach and has recovered from hypertension and Cushing’s habitus. A careful follow up is indispensable to monitor recurrence of carcinoid and complete remission of CS.

**Keywords**: Paediatric Cushing’s syndrome, Ectopic ACTH syndrome, Paediatric bronchial carcinoid

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With the submission of this manuscript, we would like to undertake that:

- The manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work.
- All authors of this research paper have directly participated in the planning, execution, or analysis of this study and have read and approved the final version submitted.
- The contents of this manuscript have not been copyrighted or published and previously and are not now under consideration for publication elsewhere.
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**Introduction**

1. **Background**- Paediatric Cushing’s syndrome (CS), a rare condition, is broadly classified, into adrenocorticotrophin (ACTH) dependent and ACTH independent CS. When the source of ACTH production is outside pituitary, it is also called as, Ectopic ACTH syndrome (EAS). The complete remission of Cushing’s syndrome is a rare phenomenon, which was achieved successfully in our patient by multidisciplinary approach and she has recovered completely from hypertension and Cushing’s habitus. The timely diagnosis of cause of hypercortisolism and its appropriate management is the cornerstone of successful management.

2. **Material and Methods**- Literature review was performed from the oldest available report in English to analyse all cases of Bronchial Carcinoid causing Ectopic ACTH syndrome in children by searching online databases (PubMed/Medline, Google Scholar and Google) for the following keywords—"Ectopic ACTH Syndrome in children”, “Bronchial carcinoid in
children” and “Cushing’s Syndrome in children”. We included the articles that described the pediatric patients of Bronchial Carcinoid causing Ectopic ACTH syndrome and reviewed the variables like age, sex, type of carcinoid, diagnosis, surgery and recurrences. We also describe a teenage girl of Ectopic ACTH secreting bronchial carcinoid who presented to us with symptoms and signs of CS.

3. Observation-
We found 14 pediatric and adolescent patients with Bronchial carcinoid causing EAS from 9 case series and reports [1-9] with mean age of 15.8 years ranging from 10-20 years. There were 9 females and 4 male children; one atypical carcinoid and four typical carcinoids; mostly involving right lung; lymph node metastasis in 6 patients. All of them were managed by surgical excision of tumour, although one patient underwent bilateral adrenalectomy due to relapse, two patients had bilateral adrenalectomy and one patient underwent hypophysectomy prior to surgery. There is one death reported and three patients had recurrences.

Another major series of ninety patients of EAS reported by Ilias et al [10] from National Institutes of Health, Bethesda, Maryland, included 35 patients of bronchial carcinoids causing EAS but the age ranged from 8-72 years (Table 1) with almost half of the patients having lymph node involvement requiring lymph node dissection with three deaths and two relapses reported.

3.1 Case report-
A 12 year old, female child presented with complaints of excessive weight gain, dry skin and weakness of limbs. There was no history of steroid intake or previous illness. On examination, she showed classical Cushing's habitus including “moon face”, abdominal striae, and hirsutism growth retardation, muscle weakness, dry and thick skin and excessive hair growth all over body (Fig 1a).

She was hypertensive (130/90 mmHg) with BMI of 22.7 kg/cm² (Ht- 134.5 cm, Wt= 41 kg) with standard deviation score (SDS) of 1.22. Her SDS for height for age and weight for age were -2.2, and -0.10 respectively. On evaluation, her midnight and evening serum cortisols levels were high (Table 2), low dose dexamethasone suppression test (LDDST) was done to confirm Cushing syndrome again showed non-suppressed serum cortisol (26.94 µg/dL). High dose dexamethasone suppression test (HDDST) showed <50% suppression (baseline serum cortisol = 59.55 µg/dL; Suppressed cortisol= 35.67 µg/dL). Bilateral inferior petrosal sinus sampling (BIPSS) was done to localise ACTH secretion with stimulation by Desmopressin 10 I.U. intravenously. It ruled out pituitary secretion and suggested peripheral ACTH secretion (Fig 1b). To identify peripheral ACTH secreting tumour, contrast enhanced computed tomography (CECT) thorax and abdomen were done which revealed a 1.5 cm nodule was detected in apical segment of upper lobe of right lung with no mediastinal lymph node enlargement (Fig 1c and 1d). The abdominal viscera and adrenals were normal. The core needle biopsy of the lung nodule was inconclusive on two separate attempts.

After management of hypokalemia and hypertension, she underwent right upper lobectomy as the location of tumour did not allow segmentectomy (Fig.2a). The histopathological examination showed well circumscribed tumour with nest of small cells around bronchial cartilage (Fig.2b) and no nuclear atypia or mitotic activity. On immunohistochemistry (IHC), the cells were immune-reactive for synaptophysin and chromogranin-A (Fig.2c) suggesting typical bronchial carcinoid.

Patient had vomiting in immediate postoperative period for which hydrocortisone was started and tapered over a period of 1 week. There was persistent hypertension postoperatively for which calcium channel blocker and B-blocker was continued. The patient became eucortisolemic 3 days after surgery with cortisol level of 7.68 µg/dL (Table 2). In six months of follow up, she lost 10 kg of body weight, facial puffiness and body hairs have decreased and she is off antihypertensives and steroids now (Fig 2d). She also has normal serum calcium,
phosphorus, parathormone (PTH) and Insulin like growth factor (IGF-1 = 355.7 ng/ml). X-ray chest shows expansion of right middle and lower lobe to occupy chest cavity.

4. Discussion

4.1 Endogenous Cushing’s syndrome (CS)

Endogenous Cushing’s syndrome (CS) is a rare disorder in children and adolescents due to increased glucocorticoids, which is more common in males in early childhood with female preponderance in older children [11,12]. The most common cause for CS is iatrogenic due to administration of exogenous glucocorticoids [13,14]. The causes of endogenous CS are classified into ACTH dependent and ACTH independent CS. (Table 3)

In ACTH-dependent causes of CS, when the ACTH is produced by pituitary adenoma, it is called as Cushing’s disease (CD). It is most common cause of CS in children older than 6 years of age and responsible in 75-90% of paediatric CS [11, 14]. Adrenal causes of CS are more common in young children and may present with features of virilisation [11,16,17]. The less common cause is where ACTH, is secreted by non-pituitary tumor, which is called as Ectopic ACTH syndrome (EAS) [14]. EAS in young children is much rare than adults where it accounts for 15% of the cases [8].

Patients of CS can present with various signs and symptoms which differ for different age and causes of CS [13]. Growth failure and associated weight gain are most common presenting features of paediatric CS [13,15]. Other common feature are hypertension (50-60%), hirsutism (80%) and striae [15].

The differentiation between ACTH dependent and independent causes of CS is done by 8 am plasma ACTH concentrations. A value of ACTH >29 pg/mL has a sensitivity of 70% to diagnose ACTH dependent cause of CS [11]. To identify the cases of CD, Corticotrophin-releasing hormone (CRH) test and the HDDST are useful but they are not reliable to differentiate between CD and other causes of ectopic ACTH secretion as patients with ectopic CS may also show a decrease in cortisol level which also happened in our patient [8,13,18]. Bilateral Inferior petrosal sinus sampling (BIPSS) is considered to be the gold standard in distinguishing CD form ectopic ACTH syndrome and for lateralisation of lesions [8, 13, 18]. In our patient, BIPSS gradients confirmed that there was no lesion in pituitary and there is ectopic secretion of ACTH.

If ACTH independent CS is diagnosed, adrenal CT or MRI is required to differentiate between adrenocortical tumour and primary nodular hyperplasia. When ectopic ACTH secreting lesion is suspected, CT neck, thorax, abdomen and pelvis is done to localise the lesion. Octreotide scan, positron-emission tomography (PET), DOTATE scan and octreotide PET scan can also help in identification of lesion [11,18]. In our patient CT thorax with using 0.5 cm cuts identified lesion of 1.5 cm in apical segment of upper lobe of right lung, which was the source of ectopic ACTH secretion.

4.2 Ectopic ACTH syndrome

Ectopic ACTH syndrome is very rare in children as compared to adults and is more common in female children of 10 year of age [11,13]. Majority of them result from carcinoid tumours of bronchus or thymus [9] but they are reported from appendiceal, kidney and duodenal also [10,19]. EAS may also occur due to ACTH secretion from adrenal neuroblastoma, clear cell sarcoma, pancreatic tumour, gastrinoma, pheochromocytoma, wilm’s tumour and sacrococcygeal tumour [10,20-25]. Muscle weakness, hypertension and hypokalemia is significantly more common in patients with EAS as compared to those with CD [8,10]. Also, when compared to CD, patients with EAS have statistically significant higher levels of urinary free cortisol, ACTH (sensitivity 80% and specificity 74% for ACTH levels of 1.6 upper limit of normal) and mean ACTH increase is lower on CRH testing (sensitivity 83% and specificity 81% for differential increase of 31% in plasma ACTH) [8]. Inferior petrosal sinus sampling is considered as gold standard for diagnosis of EAS [10]. The localization of ACTH secreting
tumor is difficult and CT, MRI and octreotide scan, all should be used for screening of EAS [10]. Although biochemical tumor markers are less helpful but serum calcitonin can be used as it is known to be elevated in carcinoids, medullary thyroid cancer and neuroendocrine tumors and is normal in CD [10]. The surgical resection of ACTH producing tumor is optimal treatment but bilateral adrenalectomy is required in refractory cases to control hypercortisolemia [10].

4.3 Bronchial carcinoids in children

Although, bronchial carcinoid are most common intrabronchial primary tumour in children [9,26] only 4% of them are associated with Cushing’s syndrome [27]. Bronchial carcinoids can arise from main, lobar or segmental bronchi and they can present with obstructive symptoms like atelectasis, dyspnea, pleuritic pain or obstructive pneumonitis [28] although our patient did not have any respiratory symptoms. Carcinoid tumors arise from Kulchitzky cells found in basal layer of bronchial epithelium. The overall incidence is 3–5 tumours per million people per year but incidence of bronchial carcinoids in children is not known but they constitute 70-80 percent of all primary malignant lung tumors in children [2,27,29].

Contrast-enhanced CT of the chest, with 5mm thick sections or MRI of neck, chest and abdomen is considered first line for diagnosing ectopic ACTH secreting lesions [18,27,30]. In our patient, the suspicious lesion was detected on CT chest with 5mm sections. Octreotide scan is useful to diagnose primary lesion and to detect metastasis and recurrences of carcinoids [9,29] but some studies suggested it to be less helpful in bronchial carcinoids as 1/3rd of them do not express somatostatin receptors [31].

Grossly, the cut surface is homogenous tan colour with foci of haemorrhage and microscopically they are composed of small uniform cells arranged in mosaic pattern with interlacing fibrovascular stroma [32]. Their average size is 2-4 cm and tumour may infiltrate the bronchial wall and surrounding lung tissue [33]. The prognosis depends upon histology, lymph node status and size of tumour [30]. They are classified as atypical (10%) and typical (90%) carcinoids depending upon the presence or absence of necrosis and elevated mitotic index (>2 mitoses/HPF) [9,33]. Both of them can be positive for markers like chromogranin A and synaptophysin. Typical carcinoid tend to be central in location while atypical ones are peripheral [9]. Although, typical carcinoid considered to be benign, both the variants are capable of metastasizing to regional lymph nodes, liver, bones and brain [30, 33]. Our patient had typical carcinoid with no evidence of necrosis and low mitotic index and hence bearing good prognosis.

The treatment of choice for a bronchial carcinoid is complete surgical resection with removal of involved lymph nodes [9,27]. Lymph nodes are involved in up to 20 percent of paediatric cases of both histology [9]. The lymph node resection is more important for atypical owing to its malignant potential. Radiation and chemotherapy can be used where complete surgical resection is not possible [31]. Somatostatin analogues, interferon α and temozolomide analogues have been used in adults with advanced disease [9]. The surgery should be parenchymal preserving whenever possible and sleeve resections and bronchoplastic procedures should be considered for central lesions [34]. In our patient, it was not possible to remove the tumour while preserving the upper lobe.

The typical carcinoid has a good 5-year survival rate of 88-92% and that of atypical carcinoid ranges form 60-75% [9,28,30,35]. The ACTH secreting bronchial carcinoids are considered aggressive variants as lymph node positivity and recurrences are observed even in typical carcinoids [11,36]. Serum ACTH and tumour markers, to detect recurrences early [27], should be done in follow up of the patients yearly. CT scan of neck and chest every 6 to 12 months is required in node positive cases [9].

Although the surgical removal of source of hypercostisolaemia is treatment of choice, medical agents such as antihypertensives and inhibitors of steroidogenesis like metyrapone and
ketoconazole can be used in preoperative period to reduce the surgical risk, when surgery is contraindicated and in postoperative period when the patient is not cured by surgical resection [18]. Resolution of hypertension is more common in children as compared to adults due to vascular protective mechanism and shorter lasting hypercortisolism [37] as is seen in our patient who became normotensive within 3 months after surgery. There was requirement of postoperative hydrocortisone in our patient as she developed postoperative vomiting, headache and weakness, which was tapered and discontinued over a period of one month. This is similar to reports by other authors [18, 38] who were able to discontinue hydrocortisone within 1-2 years.

The postoperative treatment of CS is challenging with high prevalence of hypertension, increased BMI and visceral fat mass, impaired cognitive functions and decreased quality of life [18, 39-41]. On the contrary, our patient has lost 6 kg weight and performing well in school. However, her growth chart needs close monitoring since patient did not have CD. Post-CS treatment, growth and pubertal development monitoring is important to evaluate, as growth hormone deficiency is most common pituitary deficiency in children with CD followed by ACTH deficiency [18].

5. Conclusion

Paediatric pulmonary carcinoids causing Ectopic ACTH secretion (EAS) and leading to Cushing’s syndrome is very rare entity and the algorithm of investigations should be followed to reach to diagnosis. BIPSS is investigation of choice to differentiate it from CD and CT of neck and chest helps in localising the site of EAS tumours. Treatment is surgical resection of tumor and lymph node resection with intention to achieve negative margins and prevent as much lung parenchyma as possible. The complete remission is possible in children with EAS but bronchial carcinoids causing EAS are aggressive in nature and good follow up is indispensable to monitor for recurrences.

6. Compliance with Ethical Standards:

Funding: none
Conflict of Interest: none
Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.
Informed consent: Informed consent was obtained from parents of patient who is reported in this article. The patient underwent surgical resection with all due consent from parents and the procedure and no experimental work was conducted on her.

The contribution of the authors as mentioned below with their responsibility in the research.

1. Rahul Saxena - involved in conceptualising, analysis and interpretation of data and drafting the manuscript
2. Manish Pathak - provided substantial contributions to conception and design of study and final approval of version
3. Ravindra G Shukla- provided contributions in endocrinal management and preparation of manuscript
4. Arvind Sinha- involved in revision of manuscript and providing intellectual content for manuscript
5. Poonam Elhence - involved in pathological diagnosis and drafting of manuscript
6. Jyotsna N Bharti - involved in pathological diagnosis, preparing photographs of slides and drafting manuscript
7. Dr Pushpinder Khera- involved in radiological diagnosis, preparing photographs of imaging and drafting manuscript

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12. Storr HL, Isidori AM, Monson JP, Besser GM, Grossman AB, Savage MO. Pre-pubertal Cushing’s is more common in males, but there is no increase in severity at diagnosis. J Clin Endocrinol Metab 2004;89:3818–20


Legends
Table 1. Review of literature of Bronchial carcinoid causing EAS. TC- Typical carcinoid, AC- Atypical carcinoid, SRS= Somatostatin receptor scintigraphy, FDG-DOPA= Flurodeoxyglucose- 18-L- Dihyroxyphenylalanine, KC- Ketoconazole, f/b-followed by, f/u-follow-up
<table>
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<tr>
<th>Reference</th>
<th>S.no</th>
<th>year</th>
<th>Age</th>
<th>Sex</th>
<th>EAS tumours</th>
<th>Location</th>
<th>LN metastasis</th>
<th>Imaging</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>Ward et al.[1]</td>
<td>1</td>
<td>1983</td>
<td>16</td>
<td>F</td>
<td>BC</td>
<td>Right middle lobe</td>
<td>yes</td>
<td>CT+</td>
<td>metyrapone-Surgery</td>
<td>Transspenoidal hypopysectomy f/b wedge resection</td>
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<td>Wang et al. [2]</td>
<td>2</td>
<td>1993</td>
<td>19</td>
<td>F</td>
<td>BC</td>
<td>Right middle lobe</td>
<td>no</td>
<td>x-ray</td>
<td>Bilateral (B/L adrenalectomy f/b surgical resection</td>
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<tr>
<td>Magaiakou et al. [3]</td>
<td>3</td>
<td>1994</td>
<td>15</td>
<td>F</td>
<td>BC</td>
<td>Bilateral (B/L adrenalectomy f/b surgical resection</td>
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<td></td>
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<tr>
<td>Bhansali et al. [7]</td>
<td>7</td>
<td>2009</td>
<td>ND</td>
<td>M</td>
<td>BC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT-, SRS-, MRI+, NOR+, MIL+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2009</td>
<td>ND</td>
<td>M</td>
<td>BC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT+, SRS+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
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<tr>
<td></td>
<td>9</td>
<td>2005</td>
<td>20</td>
<td>M</td>
<td>TC 2 in no</td>
<td>Surgery</td>
<td>yes</td>
<td>CT-, SRS-, MRI+, NOR+, MIL+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1996</td>
<td>19</td>
<td>F</td>
<td>TC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT+, SRS+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
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<tr>
<td></td>
<td>11</td>
<td>1995</td>
<td>13</td>
<td>M</td>
<td>TC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT+, SRS+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
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<td>12</td>
<td>1995</td>
<td>15</td>
<td>F</td>
<td>TC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT-, SRS+</td>
<td>KC+ Mitotane+, B/L adrenalectomy, Surgery when identified</td>
<td>alive after 16 yr of f/u</td>
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<td>13</td>
<td>1988</td>
<td>13</td>
<td>F</td>
<td>AC</td>
<td>Surgery</td>
<td>yes</td>
<td>CT, MRI</td>
<td>lobetomy and LN dissection</td>
<td>3 deaths</td>
</tr>
<tr>
<td>Potter SL et al. [9]</td>
<td>14</td>
<td>2018</td>
<td>20</td>
<td>F</td>
<td>BC</td>
<td>Right lower lobe</td>
<td>not assessed</td>
<td>CT</td>
<td>wedge resection</td>
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<tr>
<td>Ilias et al. [10]</td>
<td>35</td>
<td>19M</td>
<td>15</td>
<td>TC</td>
<td>4- right upper lobe</td>
<td>CT, MRI</td>
<td>17 localised</td>
<td>lobetomy and LN dissection</td>
<td>3 deaths</td>
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Table 2. Investigations of our patient

<table>
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<tr>
<th>Investigations</th>
<th>Patient Values</th>
<th>Reference values</th>
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</thead>
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<tr>
<td>Midnight serum Cortisol</td>
<td>17.52 µg/dL</td>
<td>&lt;7.5 µg/dL[11]</td>
</tr>
<tr>
<td>Evening serum cortisol</td>
<td>59.47 µg/dL</td>
<td>1.8-6.5 µg/dL</td>
</tr>
<tr>
<td>LDDST (Post 1mg Dexamethasone on 8:00 am)</td>
<td>26.94 µg/dL</td>
<td>&lt;1.8 µg/dL [11]</td>
</tr>
<tr>
<td>HDDST</td>
<td>35.67 µg/dL</td>
<td>1.8-6.5 µg/dL</td>
</tr>
<tr>
<td>ACTH (Adrenocorticotropic Hormone, Plasma)</td>
<td>76.3 pg/mL</td>
<td>&lt;29 pg/mL [11]</td>
</tr>
<tr>
<td>Serum cortisol (morning sample postoperative day 3)</td>
<td>7.68 µg/dL</td>
<td>4.5-24.0 µg/dL</td>
</tr>
<tr>
<td>Serum cortisol (morning sample 6 months postoperative)</td>
<td>3.27 µg/dL</td>
<td>4.5-24.0 µg/dL</td>
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</table>

Table 3. Causes of Endogenous Cushing’s syndrome in children. PPNAD- Primary pigmented adrenocortical disease, MEN- Multiple Endocrine neoplasia [13].

<table>
<thead>
<tr>
<th>ACTH dependent CS</th>
<th>ACTH-independent CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cushing’s disease</td>
<td>1. Adrenocortical tumours</td>
</tr>
<tr>
<td>(ACTH secreting pituitary adenoma)</td>
<td>(adenoma or carcinoma)</td>
</tr>
</tbody>
</table>
2. Ectopic ACTH syndrome

- PPNAD, Carney complex/MEN
- Macronodular adrenal hyperplasia
- McCune-Albright syndrome

Fig 1. (a) pre-operative photograph of patient showing Cushingoid facies, hirsutism and obesity (b) bilateral inferior petrosal sinus sampling with red arrows pointing the microcatheters in petrosal sinuses (c) axial and (d) coronal view of CT Chest showing a smoothly margined nodule of 15mm in apical segment of right upper lobe
Fig 2. (a) resected upper lobe of right lung, (*) tumour in apical segment (b) H&E image of nests of tumour around bronchial cartilage (*), 10x image (c) IHC for Synaptophysin, (*) showing strong cytoplasmic positivity in 40x magnification (d) postoperative photograph showing resolution of Cushing’s habitus