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Case report

A Challenging Case of Ectopic ACTH Syndrome with Bronchial Carcinoid and Literature Review

ABSEYİ SN et al. A Case of Ectopic ACTH Syndrome with Bronchial Carcinoid

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What is already known ?
Ectopic ACTH syndrome is very rare in children. It is very difficult to diagnose because it is not easily thought of. Early diagnosis is very important to prevent comorbidities and improve the patient's quality of life.

What this study adds to literature ?
Ectopic ACTH cases are mostly in the form of case reports when looking at the literature. Our case is an ectopic ACTH syndrome with broncial carcinoid. Cause it is very rare in children, we reviewed all bronchial carcinoid ectopic ACTH cases in children. Since this article collects all the cases, and the diagnosis steps were explained step by step, it will be a guide for other studies.

Abstract
Here we report an adolescent boy diagnosed with ectopic ACTH (Adrenocorticotropin hormone) syndrome (EAS) caused by atypical bronchial carcinoid. The patient was evaluated multidisciplinaryly: he had surgery and took chemotherapy and radiotherapy treatments afterward. The patient is still under our follow-up. Until today eighteen pediatric and adolescent patients with EAS because of bronchial carcinoid tumors were reported in 13 case reports and literature reviews. Ectopic ACTH syndrome caused by bronchial carcinoids is very rare in children and adolescents. Careful diagnostic evaluation and rapid treatment should be started immediately. Although complete remission is possible in bronchial carcinoids, atypical carcinoids have a more aggressive nature. A multidisciplinary approach and follow-up will improve quality of life and survival.
Keywords: Ectopic Adrenocorticotropin Hormone Syndrome, Carcinoid, Cushing

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Introduction
Endogenous Cushing Syndrome (CS) is very rare in the pediatric and adolescent periods, resulting from the overproduction of glucocorticoids (1). Every year, 3,2 cases per million persons are reported (2). Adrenocorticotropin hormone (ACTH) dependent or ACTH independent are its two basic classifications. Approximately 80 to 85% of endogenous CS is ACTH-dependent and of these 75-80% is caused by ACTH-producing pituitary adenoma (Cushing disease). Ectopic ACTH syndrome (EAS), consisting of nearly 15% of all CS cases, results from the production of ACTH from an ectopic source in the body (mostly neuroendocrine tumors) (1,3). Adrenocorticotropin hormone-secreting neuroendocrine neoplasms are usually located in the thymus, lungs, pancreas, and gastrointestinal system, but also can be presented with Ewing sarcoma, pheochromocytoma, and medullary thyroid carcinoma (4).
Bronchial carcinoids that arise from bronchial mucosal neuroendocrine cells are the most frequently seen primary malignant lung tumors and also the most common reason of EAS in children (5). These neuroendocrine tumors are well differentiated, and the word "carcinoid" distinguishes them from poorly differentiated ones, which include small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinomas (LCNECs). They are subdivided into 2 groups based on malignancy potential, with a majority of pediatric patients presenting with typical carcinoids (TC) and atypical carcinoids (AC) (6). The median age of presentation of EAS cases is 9.5 years, with a female predominance (7). Cushing syndrome diagnosis is not considered in the first place according to anamnesis and physical examination of pediatric cases. Because EAS constitutes a very small part of the etiology, the diagnosis and treatment process may be delayed. We discuss a case of an ectopic ACTH-secreting bronchial carcinoid that has previously been observed in several places; CS was not taken into consideration, despite the scheduled gynecomastia procedure, and we examine the literature currently available for pediatric instances of EAS caused by bronchial carcinoid.

Case
A 13.7-year-old boy complained of gynecomastia and too much weight gain. In his anamnesis, it was learned that he had been examined in different centers for gynecomastia for about 1 year, and even an operation was planned. There was no prior physical sickness or steroid use.
On physical examination, weight was 61 kg (0.55 SDS), height was 157 cm (-0.81 SDS) and body mass index was 24,7 kg/m^2 (0.9 SDS). His blood pressure was 95/65 mmHg (75-90th centile). The child had moon facies, truncal adiposity Buffalo hump, purple striae over the abdomen and breast, hypertrichosis, and gynecomastia (Photo 1). He had pubic hair stage 3 with a stretched penile length of 7 cm and bilateral testicular volume of 10 mL each. The other systemic examination was unremarkable. The biochemical evaluation revealed normal liver and renal function tests and lipid profiles. On the hormonal evaluation serum ACTH level was 60,2 pg/mL (N: 7.2-30 pg/mL) and basal cortisol was 20,4 mcg/dL. His midnight and evening serum cortisols concentrations were 19,9 µg/dL and 25,1µg/dL. Cushing syndrome was confirmed using a low-dose (1 mg) dexamethasone suppression test (LDDST), which revealed non-suppressed blood cortisol (19,8 g/dL). Twenty-four-hour urinary free cortisol levels (UFC) were elevated (2760 nmol/24-hour and 3800 nmol/24-hour). A high-dose dexamethasone suppression test (HDDST) showed no suppression (baseline serum cortisol=19,2 µg/dL; cortisol after test = 22,1 µg/dL). The serum level of chromogranin-A was elevated (191 ng/mL, normal: <100). Dynamic contrast MRI of the pituitary was normal.

Contrast-enhanced computed tomography (CT) of the thorax and abdomen was performed to identify the peripheral ACTH-secreting tumor. This revealed a 21x12mm hypodense homogeneous solid lesion in the left hilus and a 7mm nodule in the lingula of the left lung with micro mediastinal lymph node enlargements. To further investigate this lesion, ^{68}Ga- DOTATATE positron emission tomography (PET)/CT was done, which revealed pathological activity on the hilus and lingula of the left lung (Photo 2). This finding strengthened the possibility of the lesion being the source of EAS. A biopsy performed on the lesion under the endobronchial US revealed findings consistent with a carcinoid tumor (strongly positive ACTH antibody). The patient underwent surgery. The lesion in the hilus was dissected as much as possible from the surrounding tissues (because of its proximity to the main bronchi and vascular structures) and removed en bloc, and wedge resection was done for the lesion in the left lung. In the histopathological examination of the lung, proliferation consisting of cells with spindle-oval-shaped chromatin in the form of salt and pepper appearance, showing solid and insular organization, was observed. On immunohistochemistry, Tumor cells were positive with Chromogranin-A, Synaptophysin, CD56, TTF-1(thyroid transcription factor), and ACTH, suggesting a neuroendocrine tumor. The Ki67 proliferation index was 2-3%. Up to 5 mitoses were counted under 10 magnification with pHH3 (phosphohistoneH3).

The postoperative first-day ACTH level of the patient decreased to 14,6 pg/mL. The patient was initiated on hydrocortisone replacement (10 mg/m^2/day) and monitored every month with morning serum cortisol and ACTH and tapered over 3 months. Because of incomplete resection of the lesion, radiotherapy and 6 cycles of chemotherapy (carboplatin and etoposide) treatment were given. In the first year of follow-up, his midnight and evening serum cortisols concentrations were 1,4 µg/dL and 0,55 µg/dL, respectively. A low-dose dexamethasone suppression test showed suppressed serum cortisol (0,5 µg/dL). Twenty-four-hour UFC was 41 nmol/24-hour. The pathological activity involvement was reduced in the control 68Ga- DOTATATE PET/CT. He had no new metastasis. In his last control follow-up (postoperative fifteenth month), he was 15.2 years old, his weight was 47 kg (-1.8 SDS), height was 171cm (-0.01 SDS) and his body mass index was 16 kg/m^2 (-2 SDS). He had pubic hair stage 4 with a stretched penile length of 8.5 cm and bilateral testicular volume of 15 mL each. In the laboratory examination, there were no endocrine abnormalities such as growth hormone deficiency, thyroid dysfunction, gonadal suppression, or hyperglycemia. The physical examination findings related to CS, especially gynecomastia, were regressed (Photo 3). Pediatric endocrinology, pediatric oncology, radiation oncology, thoracic surgery, nuclear medicine, and radiology departments continue multidisciplinary follow-up. The endocrinology department performs anthropometric and hormonal (glucose metabolism, ACTH, cortisol, lipid metabolism, bone metabolism, puberty evaluation, and other endocrinologic pathologies that may accompany) evaluations every 3 months. Oncology and radiation oncology departments use laboratory and imaging methods for remission or metastasis after chemotherapy and radiotherapy treatments. Nuclear medicine and radiology departments interpret tomography and PET/CT images and jointly decide on the frequency of the tests to be performed.

Literature search

Until today, eighteen pediatric and adolescent patients with EAS because of bronchial carcinoid tumors were reported in 13 case reports and literature reviews (5,6,8-10,12-18,20). The mean age of reported patients was 14,1±2,7 years. There were 11 females (61%) and 6 males (39%). One case was not specified. Two cases were defined as atypical carcinoids. Lymph node metastasis was observed in seven patients. All of the patients had thoracic surgery, also three had bilateral adrenalectomy operations (Table 1).

There were two more major series of ectopic ACTH syndrome. In the first one, the ages ranged between 8-72 years and there were 35 patients with bronchial carcinoid tumors. Three deaths and four relapses were reported (11). In the second series, the ages ranged between 12-74 years There were 81 patients with bronchial carcinoid tumors and 26 deaths were reported (19). However, the number and outcome of the treatment follow-up of the pediatric cases in these case series were not reported.

Discussion

Cushing syndrome is very rare in children. The subtle, progressive nature of the disease and the difficulty of the testing often result in a long delay in CS diagnosis. Clinical suspicion based on anamnesis and physical examination is the initial stage in the diagnosing process. Screening and diagnostic procedures for CS evaluate the level of cortisol secretion. These procedures include the late-night salivary/serum cortisol test, the overnight 1-mg dexamethasone suppression test (LDDST), the 24-hour UFC, and the LDDST (21). The gold standard for identifying hypercortisolemia is to measure cortisol at midnight with an intravenous catheter inserted; a cortisol level exceeding 4.4 mg/dL at that time ensures a high sensitivity and specificity for CS. Diurnal testing, however, necessitates an overnight hospital stay and has a limited role in standard screening tests. A serum cortisol <1.8 µg/dL at 0800 h in the morning after LDDST is considered a normal response. The 24-hour UFC threshold value is 90 mcg/24 hours (RIA)(Radioimmunoassay) or 50 mcg/24 hours (DHPLC/ICMA) (denaturing high-performance liquid chromatography/immunochemiluminescent). Anorexia, chronic and severe obesity, pregnancy, chronic activity, depression, poor diabetes control, anxiety, malnourishment, and too much water consumption are all pseudo-cushing states that can result in false positive elevations during 24-hour UFC measurements. All of these tests have limits, and additional tests are typically required to confirm the diagnosis because none of them has 100% diagnostic accuracy (3). In our case, firstly Cushing syndrome diagnosis is confirmed by demonstrating elevated midnight cortisol (lack of diurnal rhythm), insufficient suppression in low-LDDST, and elevated 24-h UFC. Once CS diagnosis is confirmed, serum ACTH level should be evaluated to distinguish ACTH-dependent (Cushing disease or ectopic ACTH) and ACTH-independent CS. Children with an ACTH-dependent type of the syndrome can be identified with a sensitivity of 70% using a spot morning plasma ACTH level more than or equal to 29 pg/mL (3). The patient had high serum ACTH level so-called ACTH-dependent CS. Ectopic ACTH syndrome in children is uncommon compared to adults (5). Its diagnosis is a significant clinical practice challenge. In both children and adults, the diagnostic procedure to distinguish EAS from a pituitary adenoma is the same (3,7). Cushing disease and EAS can be distinguished using the desmopressin or corticotropin-releasing hormone (CRH) stimulation test, the high-dose dexamethasone suppression test, and bilateral inferior petrosal sinus sampling (BIPSS). Combining the tests with MRI is a noninvasive strategy (21). Hypophyseal and cerebral MRIs were performed because pituitary adenoma in children is the main cause of ACTH production. In ACTH-dependent CS, whole-body imaging using computed tomography (CT) should be performed after hypopituitary imaging to seek an ectopic cause (21) In our case, CT of the thorax and abdomen showed a solid lesion in the left lung after normal hypopituitary MRI results. It is challenging to pinpoint the location of the ACTH-secreting tumor, and a single positive imaging study could indicate a falsely positive result. An octreotide scan could validate EAS (5,11). According to a recent meta-analysis, both 68Ga-DOTA-peptide and 18F-FDG (fluorodeoxyglucose) are very sensitive in identifying pulmonary carcinoids, but 68Ga-DOTApeptide is more sensitive than 18F-FDG (90.0% vs. 71.0%) (22). In our case, ^{68}Ga- DOTATATE PET/CT revealed pathological activity on the hilus and lingula of the left lung. Despite having the highest sensitivity and specificity, BIPSS was not necessary for our patient since we were able to make the correct diagnosis using precise, concordant biochemical and radiological investigations.

Biopsy confirmed a carcinoid tumor and the pathologic examination revealed it as an atypical carcinoid tumor. The most frequent primary malignant lung tumor in children is bronchial carcinoid, and 4% of these tumors include CS. Histopathological analysis supports the diagnosis. Depending on the presence or absence of necrosis and an increased mitotic index (> 2 mitoses/HPF), they are categorized as atypical (%19) and typical (%90) (5,6). Biomarkers such as synaptophysin and chromogranin A may be positive in either kind. All bronchial carcinoids are best treated surgically, and when feasible, lung-sparing resections (such as wedge, segment, or sleeve resections) are advised for children and adolescents (6,23). Lymph node resection is recommended in both types but is important especially in atypical carcinoids because of its malignant potential (5). Somatostatin-based treatment, cytotoxic chemotherapy, and/or radiation should all be considered in

cases with unresectable tumors (5,24). In our case, incomplete resection could be done but the lymph node resection was done as suggested in the literature. Inhibitors of steroidogenesis like metyrapone and ketoconazole, as well as anti-glucocorticoid medications (mifepristone), can be used to treat hypercortisolemia when contraindication of surgery is present or when the patient has not recovered from surgical resection after surgery (5,25,26). The tumor's size, lymph node status, and histology all affect the prognosis. Atypical carcinoid tumors have a worse 5-year survival rate of 60–75% in pediatric series while having an excellent 5-year survival rate of 88–92% for typical carcinoid tumors (5,6,23). In a research by Degnan et al, aggressive characteristics of atypical carcinoids were shown in the pediatric cohort, and two of the five bronchial carcinoids were shown to have a higher prevalence of metastatic illness (24). Bronchial carcinoid tumor recurrence was shown to occur in 10% of cases in an investigation of the National Cancer Database (n = 3335) (3% in typical carcinoid and 25% in atypical carcinoid) (27). Lou et al defined post-resection recurrence rates of %5 for typical carcinoids and %20 for atypical carcinoids (28). According to studies, the hypothalamic-pituitary-adrenal axis may be inhibited for up to a year following Cushing's disease surgery. After the removal of the tumors that caused Cushing syndrome, including ectopic ACTH syndrome, glucocorticoid replacement treatment is thus continued for many months to a year, and occasionally even longer (25,29). According to a research, the length of tertiary adrenal insufficiency varied depending on the origin of the condition: it was shortest in cases of ectopic CS, intermediate in cases of CD, and longest in cases of adrenal CS brought on by cortisol-producing adenoma (30). In our case, we were able to cut the hydrocortisone treatment after 3 months.

Patients being treated for atypical carcinoid or typical carcinoid with positive lymph node involvement should have CT surveillance (28). The sensitivity of [68Ga]-DOTATATE for ectopic CS localization in diagnosis is high for both occult primary tumors and metastatic lesions (31). However, there is ongoing debate over the use of PET/CT in assessing tumor response to therapy. Because lower uptake on PET/CT may suggest a decrease in tumor volume, but this is only true for well-differentiated neuroendocrine tumors that are positive for the somatostatin receptor (SSR). Poorly differentiated SSR-poor tumors are challenging to see on [68Ga]-DOTATATE PET/CT, but are typically well seen on FDG PET/CT due to their strong glycolytic metabolism (32).

Although a change in tumor size is a good indicator of true response, no decrease in size does not necessarily indicate no response to treatment. Because some lesions may enlarge as a result of cystic or liquefied necrosis that develops after successful therapy. If imaging is carried out a few weeks or months following therapy, such structural alterations are more frequent and may deceive the decision-maker. Radiologists should also be aware that increased cellular expression of SSR in a variety of physiological and other pathologic processes, such as the activity of the pancreatic unsinate process, epiphyseal growth plates, reactive nodes, degenerative bone disease, and changes following radiation therapy, can cause interpretation errors (32,33). Combined with anatomic imaging (CT or MRI), it is the gold standard functional imaging modality for evaluating well-differentiated neuroendocrine neoplasms (31,32).

Conclusion

Ectopic ACTH syndrome caused by bronchial carcinoids is very rare in children and adolescents. Careful diagnostic evaluation and rapid treatment should be started immediately. Although complete remission is possible in bronchial carcinoids, atypical carcinoids have a more aggressive nature. A multidisciplinary approach and follow-up will improve quality of life and survival

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

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Photo 1: Preoperative physical examination findings: Moon facies, gynecomastia, purple striae

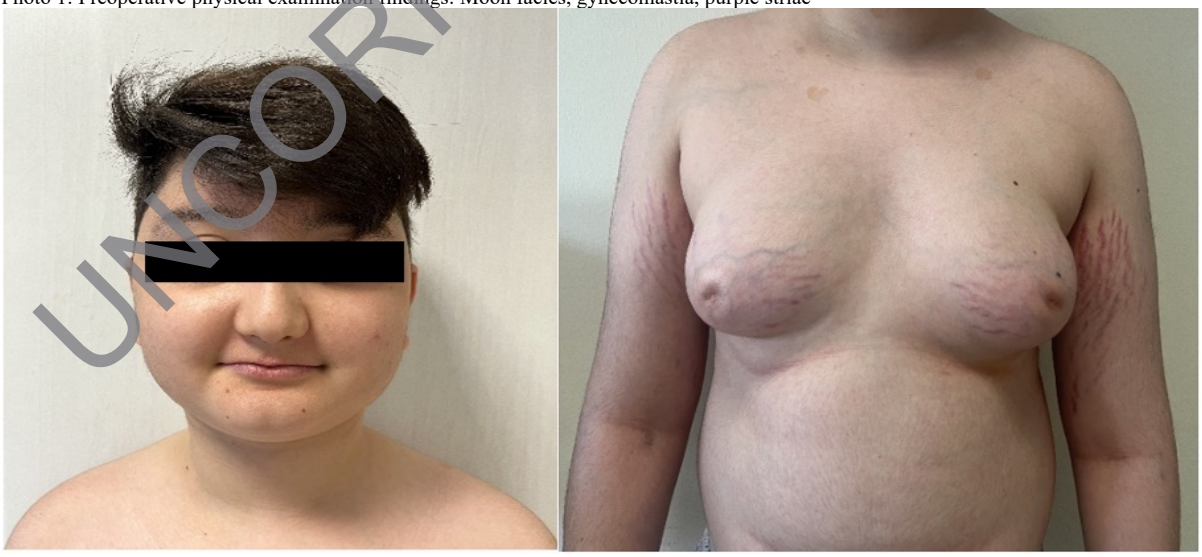

Photo 2: PET/CT images: lesion in the left lung

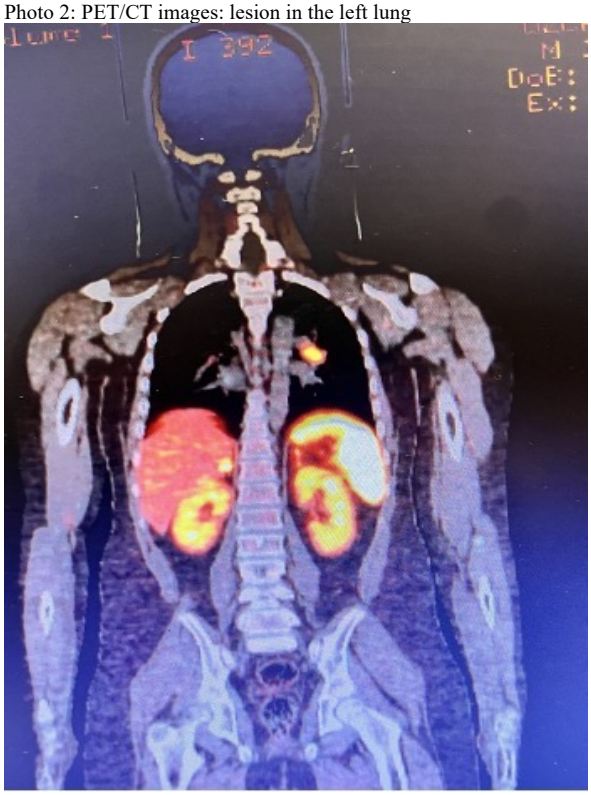

Photo 3: Postoperative regression in gynecomastia, striae, and cushingoid face appearance

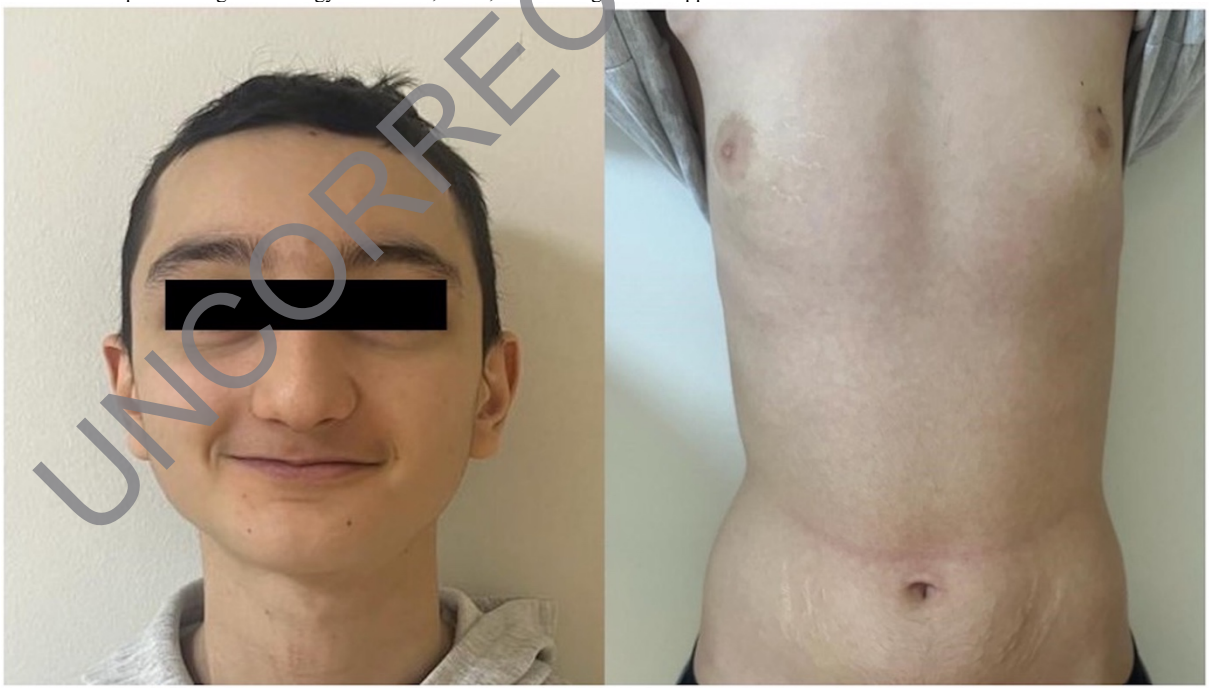

Table 1: Review of literature on bronchial carcinoid tumors causing ectopic adrenocorticotropin hormone syndrome

Reference	Year	Age	Sex	Type	LN metastasis	Treatment	RT	Outcome	Recurrence
Ward et al (7)	1983	15	F	BC		Metyrapone + surgery		6th month control normal	
Magiokou et al (8)	1994	11	F	BC		Bilateral adrenalectomy + surgical resection			
Weber et al (9)	1995	17	F	BC	+	Metyrapone + surgery	+	Well after 5 years follow up	
Ilias et al (10)	2005	8-72 years	35 patients BC		+ in 18 patients	Preoperative treatment ? + Surgery + CT in 6patients	6 patients	Death in 3 patients	İn 4 patients
More et al (11)	1988	18	M	Atypical BC	-	Ketoconazole + mitotane+ bilateral adrenalectomy +surgery		Well after 16 years follow up	-
	1995	15	M	Typical BC	+	Surgery		Well after 4 years follow up	
	1997	17	F	Typical BC	+	Ketoconazole + mitotane+ surgery		Well after 16 years follow up	4 times
	2005	16	M	Typical BC	+	Ketoconazole + surgery		Well after 3 years follow up	-
Dias et al (12)	2006	NR	NR	BC					
Bhansali et al (13)	2009	NR	M	BC		Surgery + recurrence: bilateral adrenalectomy + CT	+	Alive	1 times
		10	M	BC		Surgery - ARDS		Death	
Kakade et al (14)	2013	9	F	BC					
		14	F	BC	-	Surgery		Alive	
Goldberg et al (15)	2014	15	F	Atypical BC	+	Surgery		Well after 1 year follow up	-
Karageorgiadis et al (16)	2015	13,5	F	BC	+	Surgery (2times)			1 times
Banarjee et al (17)	2015	14	F	BC	+	RT +CT+ temezolomide+ mifepristone		Death	
Potter et al (18)	2019	13	F	BC		Surgery			
Saxena et al (5)	2019	12	F	Typical BC	-	Surgery		Well after 1 year follow up	
Golounina et al (19)	2021	12-74 years	81 patients BC			Surgery		Death in 26 patients	
Attri et al (20)	2023	17	M	BC		Surgery		Structural remission	

LN:lymph node, RT: radiotherapy, F: female, M: male, BC: bronchial carcinoid, CT: chemotherapy, NR: not reported