

Case Report of an Adrenocortical Carcinoma Associated With Germline *CHEK2* Mutation

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Adrenocortical carcinoma (ACC) is an aggressive form of cancer that originates in the cortex of the adrenal gland; the incidence of ACC is 1.5 to 2 cases per million people per year. ACCs are rare and mostly sporadic. A small proportion of ACC cases are associated with hereditary cancer syndromes. Here, we present a case of ACC with a pathogenic heterozygous germline deletion in *CHEK2* (c.1100delC). This is, to our knowledge, the first report of a patient with ACC associated with a *CHEK2* germline deletion.

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy, with an incidence of 1.5 to 2 cases per million per year. The overall prognosis is extremely poor; the 5-year staging-dependent survival ranges from 81% for patients with stage I disease to 13% for those with stage [1]. The average survival from the time of diagnosis is 14.5 months [2]. There are few effective treatment options [3]. Approximately 50% of patients diagnosed with ACC have additional complications, such as Cushing syndrome [4, 5]. Therefore, the management of ACC usually requires a multidisciplinary therapeutic approach, especially for recurrent and metastatic disease [6]. Approximately 3% to 5% of ACCs are associated with hereditary cancer syndromes, including Li-Fraumeni syndrome, familial adenomatous polyposis, Lynch syndrome, and Beckwith-Wiedemann syndrome, and in <1% of ACCs are associated with multiple endocrine neoplasia type 1 syndromes [3, 7]. In addition, ACC has been reported in patients with neurofibromatosis type 1 [8, 9], hereditary nonpolyposis colorectal cancer [10–12], and succinate dehydrogenase pathogenic mutations [13].

The *CHEK2* gene encodes a cell-cycle checkpoint kinase 2 protein, or CHK2. CHK2 plays an important role in cell-cycle regulation through interactions with other cancer susceptibility genes (e.g., *ATM*, *p53*, *BRCA1*, *BRCA2*). When activated by ATM, it subsequently phosphorylates CDC25A, CDC25C, TP53, and BRCA1 [14]. As a result, it acts as a tumor suppressor in response to DNA damage and also functions as a genetic risk modifier of other cancer susceptibility genes [15, 16]. It is hypothesized that the clinical spectrum of cancers

Abbreviations: ACC, adrenocortical carcinoma; CHK2, checkpoint kinase 2.

associated with *CHEK2* mutations may reflect their relative contribution toward the function of TP53 and/or BRCA1 [17, 18]. There are multiple *CHEK2* variants that have been associated with various sporadic cancers or familial hereditary syndromes, including large deletion of exon 9 and 10 [19, 20], 1100delC [21], missense mutations affecting the forkhead and kinase domains [22], G190A [9], A751T [23], IVS2+1G-A, and I157T [24]. However, to our knowledge, a germline *CHEK2* defect has never been reported in association with ACC. Here, we report a case of a 48-year-old woman diagnosed initially with Cushing syndrome and later with ACC, and whom was found to be a carrier of a pathogenic heterozygous deletion in *CHEK2* (namely, c.1100delC).

1. Case report

A 48-year-old woman initially came to Mary Washington Hospital in December 2010 with blurry vision, fatigue, weight gain, muscle weakness, hair loss, increased abdominal girth, abdominal striae, and indurated swelling on the back of her neck (Fig. 1). Subsequently, she was found to have an elevated morning cortisol level of 33.4 $\mu\text{g/dL}$ at 8:40 AM, a 24-hour urine free cortisol level of 498 $\mu\text{g}/24\text{ h}$ (normal range, 10 to 34 $\mu\text{g}/24\text{ h}$), and an adrenocorticotropic hormone level $<5.0\text{ }\mu\text{g/dL}$ (normal range, 5.0 to 25.0 $\mu\text{g/dL}$). The patient's salivary cortisol level was elevated at 0.99 $\mu\text{g/dL}$ (normal range, <0.01 to 0.09 $\mu\text{g/dL}$). The clinical phenotype and the biochemical findings confirmed the diagnosis of Cushing syndrome.

A CT scan of the abdomen and pelvis revealed an 8 \times 6 \times 9-cm left adrenal mass with areas of necrosis and soft tissue extending from the left adrenal vein to the level of the inferior vena cava. The patient underwent left adrenalectomy 24 August 2011, after biochemical workup excluded pheochromocytoma. After surgical resection, pathologic evaluation confirmed a high-grade ACC. The tumor was encapsulated with an MIB-1 proliferation index in 15% of the neoplastic cells, without invasion into vasculature, and was staged as a European Network for the Study of Adrenal Tumor stage II. The patient was discharged home with a replacement dose of hydrocortisone after surgery, which was discontinued after 2 months.

Two months after surgery, the patient was referred to the National Institutes of Health for further management of her cancer. She received adjuvant mitotane therapy starting at 2 g/d, increasing by 500 mg every 7 to 10 days to a total dose of 4 g/d; mitotane was well tolerated with no serious adverse effects. She also received the replacement doses of hydrocortisone and fludrocortisone and was closely monitored radiologically and biochemically every 3 months.

Unfortunately, 4 years later, a recurrence developed, identified by fluorodeoxyglucose-positron emission tomography scan (3 \times 3 cm; Fig. 2, panel I), in the prior surgical bed. The

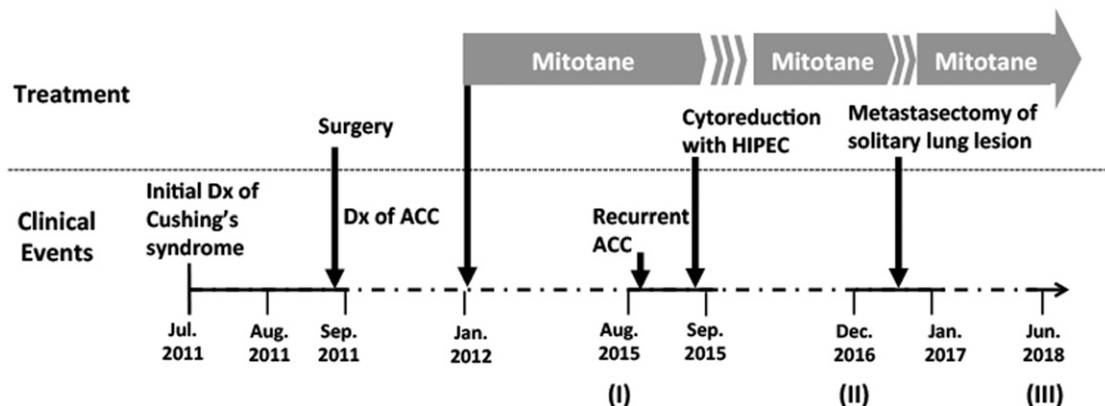


Figure 1. Clinical course. Dx, diagnosis; HIPEC, hyperthermic intraperitoneal chemotherapy.

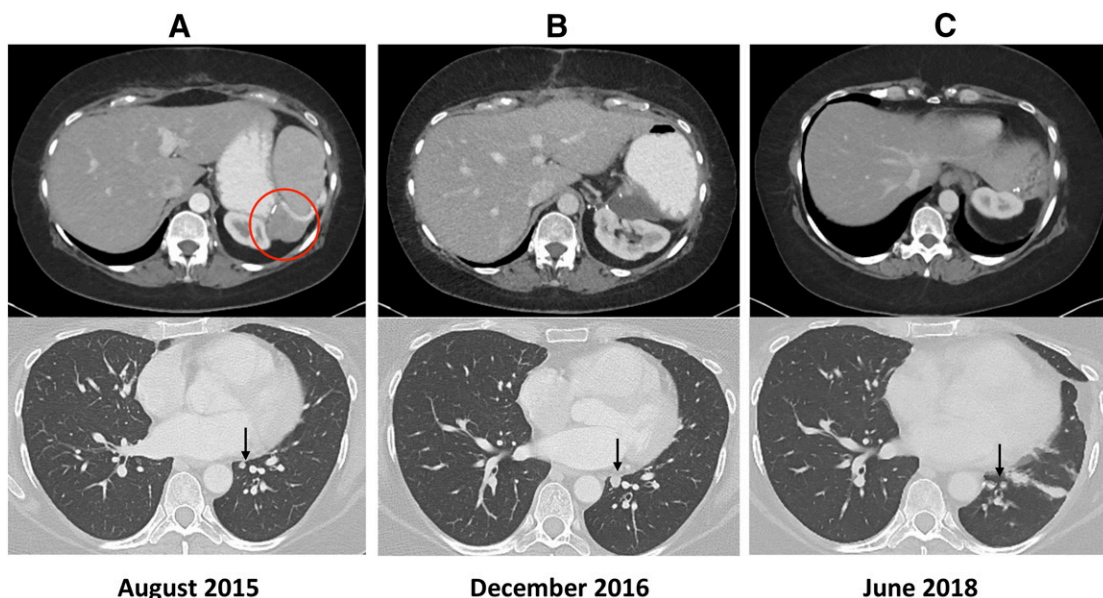


Figure 2. Radiologic response after the treatments. (A) Upper panel: Recurrent ACC on the surgical bed, indicated with circle. Lower panel: Subcentimeter lung lesion indicated at arrow. (B) Upper panel: Postsurgical change in the original recurrent site. Lower panel: enlarged lung lesion indicated at arrow. (C) Representative image showing no evidence of disease and postsurgical change.

patient was then treated with extensive surgery (including exploratory laparotomy, extensive lysis of adhesions, splenectomy, partial gastrectomy, and distal pancreatectomy en bloc with adrenal bed mass, partial omentectomy, diaphragmatic repair, and bilateral oophorectomy) and hyperthermic intraperitoneal chemotherapy with 450 mg of cisplatin. Surveillance CT scans of the chest indicated a left lower-lung nodule that grew slowly from 3×3 mm to 8×7 mm (Fig. 2, panels I and II). Subsequently, the patient underwent a left-side thoroscopic procedure to remove the solitary lesion in the left lower lobe of the lung; ACC metastases were confirmed (Fig. 3). After this procedure, there was no evidence of disease (Fig. 2, panel III). She is currently receiving mitotane without significant adverse effects.

Because of the early onset of ACC (<50 years of age), a saliva sample was sent to Invitae (San Francisco, CA) for a hereditary cancer panel. The following genes were evaluated for sequence changes and exonic deletions or duplications: *AKT1*, *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDC73*, *CDH1*, *CHEK2*, *DICER1*, *PECAM*, *FAM175A*, *FANCC*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PIK3CA*, *PMS2*, *POLD1*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RINT1*, *SDHB*, *SDHD*, *SMARCA4*, *STK11*, *TP53*, and *XRCC2*. The results revealed a heterozygous deletion (c.1100delC) of the *CHEK2* gene as the only positive finding. No tumor sample was submitted for somatic mutation test.

The patient's family history was positive for cancer; her maternal grandmother died at age 70 years of colon cancer (age at diagnosis is unknown). Both of the patient's parents are alive and in good general health; her father had a basal cell carcinoma diagnosed at age 50 years. The proband is G6P5; all children are in good general health. One daughter was tested for the *CHEK2* mutation and was negative. Genetic counseling was provided; consanguinity was denied.

2. Discussion

Here, we report an ACC case with a heterozygous deletion of the *CHEK2* gene (c.1100delC). The c.1100delC at exon 11 of the *CHEK2* mRNA leads to a frameshift of codon 367 and

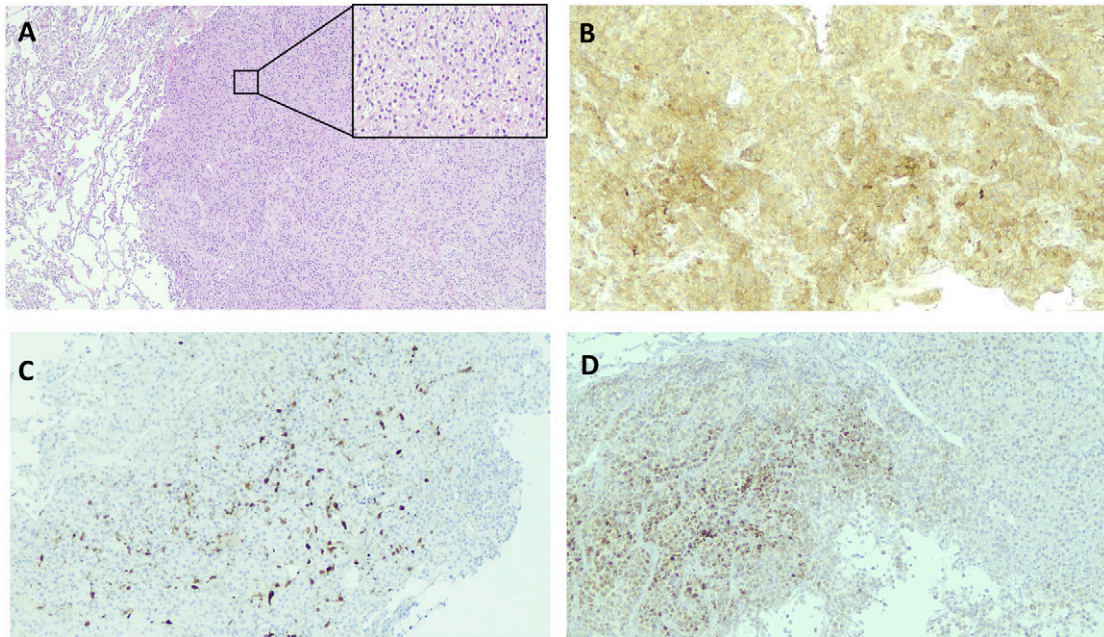


Figure 3. Pathologic evidence of ACC metastases to lung. (A) Representative hematoxylin and eosin staining of resected lung lesion, indicated on the right; normal lung parenchyma is evident on the left (magnification, $\times 4$). The enlarged section shows sheets of polygonal tumor cells with granular to clear cytoplasm, some nuclear pleomorphism, and very low mitotic rate (magnification, $\times 10$). (B) Representative immunohistochemical (IHC) staining showing diffuse inhibin expression (magnification, $\times 10$). (C) Representative IHC staining showing a patchy area positive for MELAN-A protein expression (magnification, $\times 10$). (D) Representative IHC staining showing S-100 protein expression in tumor tissue (magnification, $\times 10$).

subsequently creates a premature translational stop signal as p.Thr367Metfs*15 that is expected to result in an absent or disrupted CHK2 protein.

It is unclear if this mutation is linked to this patient's ACC tumorigenesis. However, variants with loss of function in *CHEK2* are known to be pathogenic for other cancer types [18, 21]. In a large meta-analysis of 16 studies, including 26,488 patients and 27,402 control subjects, women with heterozygosity of this variant had a relative risk for familial breast cancer of 4.8 (95% CI, 3.3 to 7.2). The cumulative risk at age 70 years was 37% (95% CI, 26% to 56%), compared to 7.8% for the average population of white women [25]. Although a study reports that the c.1100delC variant contributes an ~ 10 -fold increased risk of breast cancer in males [18], the results have yet to be validated in others [26, 27]. Patients with a history of familial breast cancer who carry the c.1100delC variant and wild-type BRCA1/2 have a considerably higher incidence of the 1-bp deletion [28]. Moreover, more patients with hereditary breast cancer with colorectal cancer carry the c.1100delC variant than do patients with breast cancer but without colorectal cancer (18% vs 4%, respectively). Nevertheless, the c.1100delC appeared to synergistically act with at least an unknown vulnerability gene and was not the major predisposing factor for the HBCC presentation [29]. Interestingly, c.1100delC carriers not only had more frequent female breast cancer in their first- or second-degree relatives, they had a higher occurrence of contralateral breast cancer and poorer distant metastasis-free survival [30]. It has been suggested c.1100delC is an adverse prognostic indicator. Nevertheless, c.1100delC mutation was found in 14 (0.8%) of 1864 Polish men with prostate cancer, in 3 of 249 Polish men (1.2%) with familial prostate cancer, and in 12 (0.2%) of 5496 healthy control subjects (OR, 5.6). In a study [31] in which effort was made to confine the incidence of cancer to those other than breast cancer from 11,116 families with a history of non-BRCA1/2 breast cancer, c.1100delC mutation primarily was associated with breast cancer but also slightly with increased overall risk of other cancers. In this study,

the ACC cases may have been underreported [31]. Findings indicate c.1100delC is a founder mutation for the aforementioned cancers [19]. To our knowledge, ours is the first report of an association between ACC and a germline defect in CHEK2.

Inactivation of the *TP53* pathway is an established feature of human cancers, with nearly all cancers evolving a system to evade this essential tumor-suppressive mechanism. Although inactivation of *TP53* through mutations or deletions of the *TP53* locus directly leads to development of various human cancers, there are many other molecular alterations that can functionally attenuate the pathway [32]. Indeed, *CHEK2* arrests the cell cycle via several mechanisms under the circumstance of DNA double-strand damage. One mechanism is phosphorylation of *TP53* by *CHEK2*, which stabilizes and activates *TP53* [17, 33]. Therefore, *CHEK2* is crucial for cell-cycle regulation, and its abnormal expression could lead to cancer independent of *TP53* mutation status [34]. More studies are needed to further clarify the role of *CHEK2* on ACC tumorigenesis.

This ACC case shows that c.1100delC of *CHEK2* may be linked to ACC tumorigenesis. Therefore, at least the *TP53* and *CHEK2* gene analyses will be informative to all patients with ACC who have a negative family history of other inherited conditions [20, 35]. The European Society of Endocrinology recommends basic clinical genetic evaluation to explore any evidence of hereditary predisposition for adult patients with ACC [36]. Specialized genetics counseling should be pursued to understand the pros and cons of genetic testing. The European Society of Endocrinology currently has no definite recommendation for somatic mutation testing of tumors [36]. If genetic testing is performed, post-test genetic counseling should follow. The finding of a germline *CHEK2* mutation may entail a clinical surveillance for patients with asymptomatic nonadrenal neoplasms.

3. Conclusions

In conclusion, we report a case showing ACC tumorigenesis is associated with a germline *CHEK2* mutation. The patient's clinical presentation and negative family history were inconsistent with the typical *CHEK2*-associated phenotype. Additional studies are needed to determine a causative role; no management recommendations can be done at this time, though close clinical surveillance will be helpful.

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