First case report of an adrenocortical carcinoma caused by a BRCA2 mutation

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Abstract
Background: Adrenocortical carcinoma (ACC) may rarely be a component of inherited cancer syndromes such as Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome. ACC caused by a BRCA2 mutation has never been reported.

Methods: Nucleotide sequencing of BRCA2 in lymphocyte and tumoral DNA of a 50-year-old male who presented with an androgen-secreting ACC and a strong family history of breast, ovarian, and pancreatic cancers.

Results: A germline BRCA2 2bp heterozygous deletion at nucleotide 8765 (8765delAG) leading to a frameshift mutation (p. Glu2846GlyfsX23) was detected. Only the BRCA2 deleted allele was retained in the ACC tumoral DNA compared with the control DNA supporting a loss of heterozygosity in the tumor.

Conclusion: This is the first reported case of a patient with ACC associated with a BRCA2 germline mutation. The loss of heterozygosity in ACC DNA suggests a causal link with the BRCA2 8765delAG mutation.

Abbreviations: ACC = Adrenocortical carcinoma, BWS = Beckwith-Wiedemann syndrome, FAP = familial adenomatous polyposis, FDG-PET = fluorodeoxyglucose positron emission tomography, LFL = Li-Fraumeni-like, LFS = Li-Fraumeni syndrome, MEN1 = multiple endocrine neoplasia type 1.

Keywords: adrenocortical carcinoma, BRCA2, TP53

1. Introduction

Adrenocortical carcinomas (ACC) are mainly sporadic, but may be found in 3% to 5% of some genetic syndromes such as Li-Fraumeni syndrome (LFS), Beckwith-Wiedemann syndrome (BWS), Lynch syndrome, familial adenomatous polyposis, and <1% of multiple endocrine neoplasia type 1 (MEN1) syndromes.1,2 Germline mutations in BRCA1 (MIM 113705) and BRCA2 (MIM 600183) genes account for cancer predisposition in families with breast and/or breast-ovarian cancer families.3 To date, BRCA2 mutation in ACC has never been reported. We describe here a case of ACC associated with a germline BRCA2 mutation in a family whose cancer history was compatible with a Li-Fraumeni-like (LFL) syndrome.

1.1. Clinical case

A 50-year-old French Canadian male with no previous medical history was evaluated for a palpable lesion in his left flank. He denied abdominal pain; his review of systems and physical examination were only pertinent for the palpable mass that was hard and nontender. Ultrasound and MRI showed a retroperitoneal mass of 18.8 × 11 × 14.9 cm (Fig. 1A, B) suspicious of an adrenal tumor. The endocrine work-up was negative except for increased levels of DHEA-S (9.9 μmol/L N: 0.5–5.5). Following surgical resection, pathology confirmed an ACC of 18 × 17 × 13 cm with negative margins (Weiss score >3) (Fig. 1C). The patient was referred to us postoperatively with a unique lytic lesion of the iliac bone discovered on fluorodeoxyglucose positron emission tomography (FDG-PET) scan. Bone CT scan and scintigraphy suggested a bone metastasis, which was confirmed by biopsy, consequently establishing a diagnosis of stage IV ACC.

The patient was offered genetic counseling; his family history revealed that his mother was diagnosed with breast cancer at 53 years old (yo). Among his maternal aunts, one developed breast cancer at 46 yo, one was affected by ovarian cancer at 61 yo, and another one had pancreatic cancer (Fig. 2). Nine female maternal cousins were affected with breast cancer between 29 and 53 yo, 2 of them were early-onset breast cancers diagnosed before the age of 35. Another cousin was suspected to be affected by an
osteosarcoma at 11 yo (Fig. 2). The 8765delAG BRCA2 mutation was identified in this family.

1.2. Molecular genetic analysis

After giving his written informed consent, the patient had genetic analysis for the 8765delAG BRCA2 mutation and the TP53 gene. Exon numbering is based on the NCBI references sequences U43746 and NC_000017.9, respectively. Lymphocyte DNA was obtained and tumoral DNA was extracted from microdissected formalin-fixed paraffin embedded ACC tumor after a 56°C overnight Proteinase K digestion in an extraction buffer (50 mM Tris–HCl, pH 7.5; 1 mM EDTA; 0.5% Tween 20, 1 mg/mL Proteinase K) using a laboratory-developed method. BRCA2 exon 20 was amplified by a polymerase chain reaction and directly sequenced (Applied Biosystems, Foster City, California, USA). TP53 gene was analyzed by multiplex ligation-dependent probe amplification and direct sequencing. The germline BRCA2 2bp heterozygous deletion at nucleotide 8765 (8765delAG) (Breast Cancer Information Core nomenclature) or c.8537_8538delAG (human genome variation society nomenclature) was identified. The deletion leads to a frameshift (p.Glu2846Glyfs) and a stop codon (Fig. 1D, G). Only the deleted allele was retained in the ACC tumoral DNA (E) compared with a nonmutated control DNA (F), suggesting a loss of heterozygosity in the tumor. (G) The frame shift changes on the amino acid sequences (amino acids in green) compared with the normal amino acid sequences (amino acids in black).

Figure 1. Abdominal MRI in sagittal (A) and transverse (B) sections of the patient showing an 18.8 x 11 x 14.9 cm mass in the left anterior pararenal space with a hyperintense signal in T1 and several hypointense nodules. (C) ACC, macroscopic picture. Nucleotide sequencing of BRCA2 gene exon 20 revealed a 2bp heterozygous deletion 8765delAG or c.8537_8538delAG leading to a frameshift (p.Glu2846Glyfs) and a stop codon in the leukocyte DNA from the patient (D). Only the deleted allele was retained in the ACC tumoral DNA (E) compared with a nonmutated control DNA (F), suggesting a loss of heterozygosity in the tumor. (G) The frame shift changes on the amino acid sequences (amino acids in green) compared with the normal amino acid sequences (amino acids in black).
1.3. Interventions and outcome

Surgical resection of the ACC metastasis was followed by irradiation. Mitotane therapy was initiated, and it was well tolerated with no serious side effects with doses escalating progressively up to 6 g/day. He was replaced by hydrocortisone (60 mg/d) for adrenal insufficiency. Unfortunately, 9 months later, 2 new hepatic lesions and 3 pulmonary nodules were identified by FDG-PET scan. He received several regimens of chemotherapy: 3 cycles of EDP (etoposide, doxorubicin and cisplatin), and then Streptozocin followed by sunitinib with no serious adverse events related to therapy. Unfortunately, therapeutic failure was evident by disease progression, so he received palliative care until he passed away 3 years after his initial diagnosis and surgery.

2. Discussion

ACC is rare with an incidence of 0.7 to 2.0 cases per million populations per year. Analyses of inherited syndromes related to ACC led to the progress in the pathogenesis of ACC including the LFS due to germline TP53 mutations, the BWS due to the deregulation of imprinted genes in the chromosome 11p15.5 region, which contains the insulin-like growth factor 2 and the closed linked H19 gene in the imprinting center 1, the Lynch syndrome due to a defect in the mismatch repair system and the Lynch syndrome due to germline APC gene mutations suggests a causal link between the BRCA2 gene and harboring the BRCA2 6174delT mutation. Both masses were removed, but no tumoral DNA was available for genetic studies. Adrenal tumors in these cases could have occurred by coincidence. In the case of our patient, loss of heterozygosity in ACC tumoral DNA as described previously in most tumors related to BRCA2 gene mutations suggests a causal link between the BRCA2 8765delAG mutation and the ACC. The simultaneous presence of TP53 gene p.Pro72Arg polymorphism and the BRCA2 8765delAG mutation may suggest a potential interaction between these 2 genetic defects. This case of ACC suggests that a detailed medical and family history may reveal an unsuspected underlying hereditary condition and should be performed in all patients with ACC. Patients should be referred for specialized genetic counseling to understand the risks and benefits of genetic testing; adequate informed consent should be obtained as well as posttest genetic counseling. Based on recent findings, in the absence of family history suggesting any other genetic conditions, at least the TP53 gene analysis should be offered to all ACC patients. Furthermore, the efficacy of ACC surveillance strategy among children found to have a TP53 mutation was proven with better outcome and survival. Thus, the identification of an unsuspected germline TP53 mutation may entail a clinical surveillance protocol for the detection of asymptomatic nonadrenal neoplasms in individuals with germline TP53 mutations.
3. Conclusions
This is the first reported case of ACC associated with a BRCA2 germline mutation. Loss of heterozygosity in tumoral DNA confirms that the BRCA2 8765delAG mutation plays a role in adrenal oncogenesis supporting that ACC may be included in the spectrum of cancer-related BRCA2 gene.

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