Clinical Characteristics of Laryngeal Cancer in BRCA-1 Mutation Carriers

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Abstract. Background: The aim of this study was to analyze the occurrence of clinical features characteristic of breast cancer type 1 susceptibility protein (BRCA-1)-dependent tumors in a series of BRCA-1 mutation carriers with laryngeal cancer. Patients and Methods: The clinical features of five laryngeal cancer patients with BRCA-1 mutations registered in our center were analyzed for: sex, age at diagnosis, age at operation, tumor size and localization, histopathological subtype and grading, lymph node and distant metastases, mode of treatment and long term results of the therapy. Results: The five patients were all men, with an average age at diagnosis of 52.4 years. The majority of the patients had clinical features typical of BRCA-1-dependent tumors: four out of the five patients had advanced staging at the time of diagnosis and in three of them the disorder disseminated within one year of follow-up. Conclusion: Since laryngeal carcinomas in men with BRCA-1 mutations show clinical features characteristic of BRCA-1 dependent tumors, it is reasonable to consider treatment modifications appropriate for this sub-group of tumors.

Breast cancer type 1 susceptibility protein (BRCA-1) mutations are associated with a very high risk of carcinomas of the breast and ovaries (1-2). Additionally, BRCA-1 mutation carriers show a moderately increased probability of developing cancer of several other organs including the colon, pancreas, prostate and stomach (3-6). Very few cases of laryngeal cancer among BRCA-1 carriers have been reported, a situation that does not allow a definite conclusion on the association between mutations and risk of cancer of the larynx (4, 5, 7-9). In this paper, the potential association between BRCA-1 mutation and laryngeal cancer was analyzed by checking the occurrence of clinical features characteristic of BRCA-1 dependent tumors in a series of laryngeal carcinomas from BRCA-1 families registered in our center.

Patients and Methods

Patients. The clinical features of five patients were analyzed. Two of them (1, 2) were identified by genotyping 430 unselected consecutive patients affected by laryngeal cancer diagnosed at the Department of Otolaryngology and Laryngological Oncology in Szczecin (Poland) from 2001 to 2006. An additional group of three laryngeal cancer patients (3-5) was collected from a general database of BRCA-1 mutation carriers at the International Hereditary Cancer Center (IHCC), Pomeranian Medical University, Szczecin, Poland. The patients in that database were selected based on their familial relationship with patients affected by other types of cancer. Thus, they cannot be regarded either as consecutive or as unselected.

The DNA obtained from peripheral blood was screened at the International Hereditary Cancer Center for the occurrence of at least one of the three constitutional BRCA-1 mutations dominant in Poland, C61G, 4153delA and 5382insC, covering over 90% of all BRCA-1 mutations in Poland. Further details are described in reports by Górski et al. (10, 11).

The clinical characteristics were recorded for all five laryngeal cancer patients who were carriers of a BRCA-1 mutation. These included: sex, age at diagnosis, age at operation, tumor size and...
localization, clinical staging, histopathological subtype and grading, lymph node and distant metastases, mode of treatment and long-term results of the therapy.

Results

The clinical and genetic characteristics are summarized in Table I.

**BRCA-1** mutation C61G was detected in 3 patients (1-3) and 5382insC in 2 patients (4, 5). All five patients were men, with an average age at diagnosis of 52.4 years (range 45-58).

In all the cases squamous cell carcinomas of the larynx was diagnosed.

In four out of the five patients (1-4) the tumor was already advanced at the time of diagnosis (stage III or IV). Two of the patients (1, 2) showed postoperative local lymph node metastasis and despite combined therapy including total laryngectomy, neck dissection to remove the local lymph nodes and postoperative radiotherapy, both died within one year after operation due to generalization of the malignancy.

One patient (3) had a tumor of size T3 without lymph node metastases, however, 6 months after laryngectomy, a metastasis in the right lung was detected. For this reason he was subjected to a partial lobectomy and postoperative chemotherapy (methotrexate). This patient has been regularly monitored (for 6 months to date) without any recurrences.

One patient (4) also showed a tumor of size T3 without lymph node metastases. After total laryngectomy and postoperative radiotherapy, he has been free of recurrences for the last seven years.

One patient (5) had a tumor of size T1 without lymph node metastases, however after a first partial laryngectomy with laserotherapy, a new tumor was detected after six years and the patient had to be subjected to a second partial laryngectomy with laser therapy.

Discussion

The present study is, to our knowledge, the first analysis of the clinical features of laryngeal carcinomas among carriers of **BRCA-1** mutations. Thus, this series of a few cases is actually unique.

The clinical features typical for **BRCA-1**-dependent breast and ovarian carcinomas were found also in the majority of the laryngeal carcinomas in the men with constitutional **BRCA-1** mutations. The carcinomas were characterized by earlier than average onset and aggressive progression. The average age at diagnosis among the **BRCA-1** carriers was 52.4 years in contrast to 58.3 years among unselected carcinoma of the larynx cases (12). Four out of the five patients had advanced staging at the time of diagnosis and three of them developed disseminated disorders within one year of follow-up.

The histopathological grading was described as 2/3 in two cases and as 2 in another two cases, however, in all of the tumors the pathologists reported a high proliferative rate of 15-45 mitoses per 10 fields 10×40.

Knowledge of the spectrum of tumors associated with **BRCA-1** constitutional mutations has potentially great clinical relevance. It has been well proven that **BRCA-1**-dependent carriers need special programs of prevention, surveillance and treatment for breast and ovarian cancer (13, 14). Especially noteworthy and promising is the very high rate of complete remissions of breast carcinomas in females with **BRCA-1** mutations following treatment with cis-platinum (15-17).

Conclusion

Laryngeal carcinomas in men with **BRCA-1** mutation show clinical features which are also characteristic of other tumors in carriers of these mutations, thus it is reasonable to consider treatment modifications for them such as participation in clinical trials of monotherapy using cis-platinum.
References

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