Solid Tumour Section
Review

Head and neck: Laryngeal squamous cell carcinoma
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Classification

Note: The larynx extends from the tip of the epiglottis to the inferior border of the cricoid cartilage. The vast majorities of malignant neoplasms of the larynx arise from the surface epithelium and are therefore classified as keratinizing or nonkeratinizing squamous cell carcinomas (SCC). Other rare malignant forms include verrucous carcinoma, adenocarcinoma, fibrosarcoma, and chondrosarcoma.

Laryngeal carcinoma infiltrates locally in the mucosa and beneath the mucosa and can metastasize via the lymphatic system and the bloodstream. According to their anatomical localization, laryngeal carcinomas could be subdivided into:
1) supraglottic carcinomas, confined to the supraglottic space and spreading interiorly into the preepiglottic space.
2) glottic carcinomas, rarely spreading into the supraglottic area but rather into the subglottic space.
3) subglottic carcinomas, often showing an infiltrative growth pattern unrestricted by tissue barriers.

Clinics and pathology

Epidemiology

Laryngeal carcinoma accounts for a small fraction of all human malignancies (less than 2%), but the incidence varies among geographically. Laryngeal SCC occurs most often in the sixth and seventh decades. Men are more frequently affected than women. The etiology is not well known, but exposure of the mucosa to a wide variety of ingested and inhaled exogenous carcinogenic agents, such as tobacco smoke, alcohol, and HPV infections greatly increases the risk of developing these tumors. Avoiding cigarettes and alcohol could prevent about 90% of laryngeal SCC.

Pathology

Histopathologically, laryngeal SCC can further be classified into: well differentiated (more than 75% keratinization), moderately differentiated (25-75% keratinization), and poorly differentiated (<25% keratinization).

Carcinoma of the supra- and subglottic larynx are more likely to be non-keratinizing and poorly differentiated, and, in general, they are often large at the time of diagnosis, and have a more aggressive behavior and tend to metastasize early (20-40% of the cases). In contrast, lesions of the true vocal cords are typically small when detected, and more often moderately to well differentiated, rarely metastasize, and tend to be associated with a better prognosis.

Cytogenetics

Note:
Chromosome abnormalities

115 laryngeal carcinomas with clonal chromosome abnormalities have been reported. In general, the karyotypes are relatively complex with a nonrandom pattern of deleted and amplified chromosome segments. This is in line with the notion that laryngeal carcinoma, like most other malignancies, develops through the accumulation of multiple genetic changes. The chromosomes most frequently involved in structural rearrangements are chromosomes 1, 2, 3, 4, 5, 7, 8, 11, 12, and 15, with breakpoints clustering to the pericentromeric regions, i.e., the centromeric bands p10 and q10 and the juxtacentromeric bands p11 and q11, accounting for 43% of the total breakpoints. The most common imbalances brought about by numerical
and unbalanced structural rearrangements are loss of chromosomal region 3p21-pter, part of or the entire chromosome arms 4p, 6q, 8p, 10p, 13p, 14p, 15p, and 17p, and gain of chromosomal regions 3q21-ter, 7q31-pter, and 8q. A total of 17 recurrent structural aberrations, mostly in the form of whole-arm translocations, isochromosomes (i), and deletions (del), have been identified. The most common among them were i(8q), i(3q), i(5p), del(3)(p11), and homogeneously staining regions (hsr), a cytogenetically detectable sign of gene amplification, in band 11q13. A subgroup of laryngeal SCC have had multiple, unrelated abnormal clones, with simple, often balanced structural rearrangements or numerical changes. These clones have always had near-diploid chromosome numbers. The finding of such cytogenetic polyclonality could be interpreted as evidence of 'field cancerization' but it cannot be ruled out that the cytogenetically unrelated clones are united by a submicroscopic, pathogenetic mutation; the cytogenetic differences would then only reflect differences in clonal evolution. The third alternative is that some of the near-diploid clones actually represent preneoplastic lesions or genetically damaged, nonneoplastic epithelial or stromal cells in the tumor surrounding.

Fluorescence in situ hybridization (FISH)
FISH analysis has recently been undertaken to verify and in detail characterize the most common recurrent chromosomal changes in head and neck SCC (HNSCC), including laryngeal SCC. FISH has demonstrated that cytogenetically detectable hsr in these tumors almost always corresponds to amplification of DNA sequences originating from 11q13, and the amplicons mapped vary in size from 3.5 to 4.5 Mb with a core of 1.5 - 1.7 Mb, and often many oncogenes in this region are coamplified, including CCND1, FGF3, FGF4, EMS1, and SHANK2. Another finding is that the amplification of 11q13 is often concomitant with deletion of distal 11q. The latter finding indicates that not only the amplification of one or more dominantly acting oncogenes in 11q13, but also loss of a tumor suppressor gene in the distal part of 11q, are critical for the development of laryngeal SCC. Detailed FISH characterization of pericentromeric rearrangements, in particular for chromosomes 1 and 8, with the use of YAC clones spanning the pericentromeric region of chromosomes, suggest that the essential outcome of these rearrangements at DNA level is the resulting genomic imbalances, i.e., loss or gain of neoplasia-associated genes. Furthermore, more precise mapping of breakpoints on chromosomal arms 1p and 8p has delineated critical regions for deletions within 1p11-p13 and the subtelomeric region of 8p.

Genetic imbalances revealed by CGH, allelotyping, and LOH studies
A large scale effort has been devoted to the identification of tumor suppressor gene loci and amplified oncogenes in laryngeal carcinomas. Earlier loss of heterozygosity (LOH) studies focused on specific chromosomal arms pointed out the frequent loss of alleles from 3p, 8p, 9p, 13q and 17p in head and neck SCC (HNSCC) in general as well as in laryngeal SCC. A number of recent studies based on allelotyping or comparative genomic hybridization (CGH) indicate that HNSCC, including laryngeal SCC, display massive and widespread genomic imbalances and that certain chromosome segments are lost more often than others. Combined data in these studies indicate that the most frequent imbalances is loss of genetic material from 3p, 8p, 9p, 13q, and 17p, found in more than 50% of the cases and less frequently, deletions in 3q, 4p, 4q, 6p, 6q, 8p, 8q, 11q, 14q, 17q, 19q, and 20p observed in 30-50% of the cases. Overrepresentation of genetic material occurs often in chromosomal arms 3q, 7p, 8q, 9q, and in chromosomal band 11q13.

Cytogenetics morphological
Functional studies of genes involved by chromosomal imbalances:

Cytogenetics molecular
Tumor suppressor genes (TSG):
Chromosomal arms 3p: Partial and entire loss of 3p is one of the most common changes in laryngeal SCC detected by various techniques. A number of TSG are localized in this chromosomal arm. Among them, only FHIT was investigated in laryngeal SCC and its precursor lesions. In a recent study, decreased expression of this gene, through deletion or promoter methylation was detected in about 42% of SCC and 23% of dysplasia lesions.

Chromosome arm 8p: Loss of 8p has been mapped in detail with the use of microsatellite markers. However, no candidate TSG in this arm has so far been investigated in these neoplasms.

Chromosome arm 9p: CDKN2A (also known as p16), localized at 9p21, has been extensively investigated in laryngeal SCC. Using various detection techniques, such as immunohistochemistry and RT-PCR, it was shown that loss of CDKN2A expression, through either homozygous deletion or promoter hypermethylation, was present in 52-82 % of HNSCC, including laryngeal SCC. Furthermore, a number of studies have shown that the decreased expression of this gene was associated with poor survival in patients with laryngeal SCC.

Chromosomal arm 13q: Allelic loss of the RB1 gene, mapped to 13q14, is frequent in laryngeal SCC. Expression analysis of RB1 has yielded inconsistent results, and the role of RB1 inactivation in laryngeal SCC has not been clearly established.

Chromosome arm 17p: TP53 mutation and the alteration of its protein have been extensively studied in laryngeal SCC. These studies suggest that TP53 mutations occur early in the neoplastic transformation
of these tumors. Furthermore, a significant correlation between expression of mutated TP53 and clinical outcome has been shown in patients with laryngeal SCC; overexpression of mutated TP53 predicts poor disease-free and overall survival rates.

**Oncogenes:**

**Chromosomal band 11q13:** The pathogenetic importance of 11q13 rearrangements is supported by extensive molecular studies showing that genomic amplification of several loci within this band, including oncogenes CCND1, FGF3, FGF4, and EMS1, is found in up to 30% of primary HNSCC including laryngeal SCC. Among the genes in the amplicon, CCND1 appears to be the prime target as its overexpression has been demonstrated by various molecular techniques in about 15-60% percent of primary HNSCC. Interestingly, a recent study has shown that Cyclin D1 overexpression alone can induce extension of the replicate life span of normal keratinocytes, and the combination of cyclin D1 overexpression and TP53 inactivation led to their immortalization. Several attempts have been made to correlate cyogenetic or molecular genetic data with clinical outcome in laryngeal carcinoma patients, and it has been shown that 11q13 rearrangements and amplification/amplification of CCND1 are associated with a poor prognosis.

**Chromosome arm 7p:** Overrepresentation of partial or entire chromosome 7 has been a common finding in HNSCC and laryngeal SCC. Epidermal growth factor receptor EGFR and the insulin like growth factors IGFB1 and IGFB2 are three potentially interesting genes located in the 7p13-22 region. The EGFR gene has been extensively investigated in HNSCC and laryngeal SCC and their precursor lesions. The results of these studies suggest that amplification and/or overexpression of EGFR gene occurs in the relatively early stage of the development of HNSCC and a high level of EGFR gene accumulation probably plays an important role in the progression to invasive cancer. Furthermore, overexpression of this gene has been significantly associated with short disease-free and overall survival in HNSCC and laryngeal SCC patients.

**Chromosome 8q:** Partial or entire gain of 8q through the formation of isochromosome i(8q) and unbalanced structural rearrangements is one of the most common structural changes in laryngeal SCC. Several genes of interest, such as MYC and PTK2, are localized at 8q23-24. In a number of recent studies using FISH, tissue microarray and immunohistochemistry, a high frequency (30-68%) of MYC gain/amplification and overexpression has been observed in laryngeal SCC.

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