Merkel cell carcinoma

Pathological and molecular aspects of diagnosis and clinical features

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Merkel cell carcinoma (MCC) is an aggressive neoplasm of the skin usually developing in the elderly. The morphological and phenotypical characteristics of Merkel cell carcinoma was recently expanded by the molecular profile. The current review is a compilation of these data, which may enable better understanding of the histogenesis and potential target therapy in this rare tumour of the skin.

Key words: Merkel cell carcinoma, cutaneous neuroendocrine carcinoma, histology, immunohistochemistry.

Introduction

Merkel cell carcinoma (MCC) was originally described by Toker in 1972 as trabecular carcinoma [1]. According to his concept, MCC was referred to as a variant of sweat gland carcinoma. In 1978, Tang and Toker put another hypothesis into consideration. Relying on the ultrastructural analysis of three patients, they suggested its derivation from neural crest, implying Merkel cell as a potential cell of origin [2]. Merkel cells took their name from Friedrich Sigmund Merkel who originally described them in 1875 as mechanoreceptors that were predominantly localized in close relation to hair follicles [3]. They derive from the neural crest and have potential for both neuroendocrine and epithelial differentiation [4, 5]. The relationship of Merkel cells and MCC suggested by ultrastructural findings was later confirmed by immunohistochemical studies which showed expression of neuroendocrine markers [6-9]. The derivation of MCC from Merkel cell, although supported by these reports, is still not completely confirmed. There are still some unsettled issues. One of them is predominant development of MCC in the dermis, while Merkel cells are housed in the epidermis. However, there are a few reports of MCC showing extensive epidermotropism seemingly sharing potential of Merkel cells for intraepidermal growth [10-12]. While Merkel cells constantly express vasoactive intestinal peptide (VIP) and metenkephalin, these markers were not indentified in MCC [13]. Therefore, some authors suggest that, alternatively, MCC may derive from an immature totipotential stem cells that acquire neuroendocrine features during malignant transformation [13].

Clinical features

Merkel cell carcinoma is a rare neoplasm. Its annual incidence varies between 0.2 and 0.45 per 100 000 people [4, 14]. Most of MCC occurs in the 6th and 7th decade of life. Only 5% of reported cases develops below the age of 50 [7]. The tumour affects predominantly the Caucasian race, being exceptionally rare in black-skin people [5, 15, 16]. Due to relative rarity of the tumour, the data concerning MCC are not unequivocal [4, 17]. There is a slight predominance of males in some reports, up to 2.3 times [16, 18], whereas others show female prevalence [5] or equal incidence of both genders [4]. The largest

report [17], based on 875 cases, revealed the slight predominance of males (male/female ratio of 1.5 : 1).

Etiological factors that may play a role in MCC development include sun exposure and immunosuppression. As the tumour frequently develops on sun-exposed areas of the body, ultraviolet light (UV) has been regarded as a major risk factor for a long time [5]. This hypothesis was confirmed recently by identification of CC > TT dimeric transition mutations in p53 tumour suppressor gene which are a hallmark of UV-B-dependent mutagenic event [19]. Patients with chronic immunosuppression are also at risk of MCC as the tumour may appear in various settings: organ transplant recipients, malignant lymphoma and in patients with HIV infection or after chemotherapy for solid tumours [5, 15, 20, 21].

Recently, the hypothesis of viral aetiology as explaining the increased susceptibility for immunocompromised patients to develop MCC was validated. The well-known oncogenic virus Epstein-Barr was excluded as a potential candidate [22]. However recently Shuda *et al.* detected a virus named Merkel cell polyomavirus (MCV), that was integrated into the genome of 80% of analysed cases of human MCC [23]. This was confirmed by another study, in MCV DNA was identified in 13 of 22 cases (59%) [24].

The clinical appearance of MCC is typical, however not very specific. Taking into account the relative rarity of that tumour, the clinical diagnosis may be a challenge and always requires the histopathological analysis supported by immunohistochemical techniques (see below). Clinical differential diagnosis must include basal cell carcinoma and squamous cell carcinoma of the skin, pyogenic granuloma, melanoma, cutaneous lymphoma, eccrine carcinoma and metastatic tumours from other primary sites.

The tumour usually develops on the sun-exposed areas of the body [17-19, 25] with the head and neck region predominating (47-50%) followed by extremities (40%) and the trunk (5-10%) [13, 17]. Merkel cell carcinoma usually appears as a solitary pink to purple-red, dome-shaped, tender nodule or indurated plaque that might also be skin-coloured [13, 17]. It is painless and grows rapidly (several weeks to months). The tumour size may reach several centimetres in the largest dimension [13, 17].

The clinical behaviour of MCC is aggressive. Local recurrence occurs in 25-75% of cases, with regional lymph node involvement in 52-75% and distant metastases in 34-75% of patients [4, 15, 17]. Common sites of metastases include the liver, bones, lungs and the brain [4]. Long term 5-year survival is 30-76% [4].

Treatment of MCC requires wide surgical excision with a suggested 3 cm wide margin including superficial fascia [15]. Since the tumour is radiosensitive, radiation therapy is used as an adjuvant for the primary or in treating of the local recurrences [17].

Histopathology of Merkel cell carcinoma

Histologically, the tumour mass is usually centred in the mid-dermis and may frequently infiltrate the subcutaneous tissue. The overlying epithelium may remain unchanged, however, sometimes it may be ulcerated [7]. The tumour is composed of uniform population of small cells that have scant cytoplasm, vesicular nucleus with multiple small nucleoli [26]. The tumour has variable histological arrangement, therefore three patterns were distinguished solid – most often, trabecular and diffuse [7]. Since in most cases more than one pattern may be present, they are not widely used in pathology reports [7]. Merkel cell carcinoma is a tumour that may show epidermotropism of its cells [10, 11]; this phenomenon is uncommon as it may occur in less than 10% of cases [12]. In exceptional cases MCC may involve the epidermis without dermal component [12]. In more than half of the cases lymphovascular invasion is identified. Mitotic figures and apoptotic bodies are multiple.

Merkel cell carcinoma demonstrates expression of variable types of cytokeratins, including wide spectrum types (AE1/AE3, MNF116) and the low molecular weight (CAM5.2). Only 10% of cases were positive for CK7. Typically, cytokeratin 20 (CK20) is identified in MCC. Cytokeratin may have cytoplasmic and especially characteristic paranuclear reactivity (dot-like) in MCC. Detailed immunohistochemical analysis revealed other markers of MCC [27], CD56 (NCAM), NSE and BCL-2 were detected in 100% of cases of MCC [7, 27-30]. The neuroendocrine differentiation of MCC is supported by identification of synaptophysin and chromogranin A [27, 29, 30]. No expression of TTF-1, CD45/LCA, CD20, CD3 and CD34 is usually revealed [27]. Half of MCC cases may express topoisomerase IIα and almost all cases showed CD117 (c-kit) positivity [31].

As small cell anaplastic malignancy, MCC requires differentiation from other primary cutaneous carcinomas. Basal cell carcinoma (BCC) and squamous cell carcinomas may be distinguished basing on purely morphological grounds. These two types of skin cancers show a higher or lower degree of differentiation, whereas MCC is an undifferentiated carcinoma [32]. MCC should be distinguished from lymphomas, neuroblastoma, extraskeletal Ewing sarcoma, peripheral neuroectodermal tumour [33], but particularly important is differentiation with cutaneous metastasis of small cell carcinoma (SCC) of the lung. Metastatic SCC may be excluded by means of immunohistochemistry with applications of cytokeratin 20 (CK20) and TTF-1 (thyroid transcription factor 1) [6, 27, 33]. Merkel cell carcinoma does not

show TTF-1-positivity, while this marker is present in SCC of the lung [6, 33]. Since the pattern of staining of CK20 is reverse, it is recommended to use these two antibodies simultaneously [31, 33]. Although CK20 is a reliable, sensitive and specific marker for MCC, one should remember that it may be exceptionally absent in some cases [27, 34].

Lymphomas may be distinguished from MCC by demonstration of lymphoid markers (CD45/LCA, CD20, CD3, etc.) that are not present in MCC [7]. The diagnosis of the most common undifferentiated hematologic malignancy – acute lymphoblastic lymphoma (ALL) – may be confirmed by means of TdT (terminal deoxynucleotidyl transferase) and CD10 immunoreactivity [27]. It is important to rely on a wide spectrum of phenotypic markers as 53% of MCCs may express strongly and diffusely TdT in the tumour nuclei [27]. Extraskeletal Ewing sarcoma is CD99+ and Fli-1+, but these antigens are positive in MCC in 50% and 90%, respectively [7]. Immunostaining for cytokeratins may be helpful in this regard.

Melanoma also requires differentiation from MCC. It is positive for S100 protein, HMB-45 and melan A [16]. However, S-100 protein is not an entirely specific marker as it may be positive in some cases of MCC [7].

Regulatory pathways in Merkel cell carcinoma

Only scarce data are available referring to activation of the specific intracellular regulatory pathways in MCC. The results of these studies may alter currently used therapy in this neoplasm provided that new molecular targets are disclosed. As mentioned above, MCC is a CD117 (C-KIT) positive malignancy [31, 35-38]. Some authors reported no mutations of *KITC* [35, 38], whereas the others identified silent mutations in exon 17 only [39]. Anyway, these results precluded usage of tyrosine kinase inhibitors (e.g. imatinib) in the therapy of this tumour. Since normal Merkel cells do not express CD117, the *KITC* mutations located in other exons as those defined for gastrointestinal stromal tumours (GISTs: exon 9, 11, 13, 17) may play a role in pathogenesis of MCC [35].

Expression of growth factor receptors in MCC varies: epidermal growth factor receptor (EGFR) and HER2 were not demonstrated, while vascular-endothelial growth factor A (VEGF-A), VEGF-C, VEGF-R2, platelet-derived growth factor α (PDGF-α) and PDGF-β were identified [37-39]. Silent mutations of platelet-derived growth factor receptor A (PDGFRA) were detected in exons 10, 12 and 18 [39]. The downstream regulators of the phosphatidylinositol kinase (PI-3K) pathway were analysed. PTEN is down-regulated [37] and it seems to be dependent on epigenetic events since PTEN mutations were rarely identified in MCC [40]. The MAPK pathway that is involved in cell differentiation, apoptosis and proliferation consists of the extracellular regulated kinase (ERK) pathway, the C-Jun-NH2 terminal kinase (JNK) pathway and the P38 pathway. Whereas the ERK pathway seems to be inactive in MCC [41], phosphorylated P38 was a frequent event [37].

An aggressive behaviour of MCC depends to a vast extent on the molecular alterations. Some of them have been elucidated. The adhesion molecules may play a role in the process of metastasis and therefore they were one of potential areas of investigation. Epithelial cell adhesion molecule (Ep-CAM), neural cell adhesion molecule N-CAM (CD56), CD24 [42] have been suggested as potential markers of more aggressive clinical behaviour [9, 28].

Kurzen *et al.* showed that the expression of Ep-CAM seemed to be stronger in primary MCC that metastasized than in tumours that did not [43]. CD24 seems to be an important molecule participating in metastasis as it may bind with P-selectin (CD62P) present on the leucocytes, thrombin-activated platelets and endothelial cells [42]. Binding with leukocytes and platelets may protect the circulating tumour cells from destruction and anchorage onto the endothelial cells may commence transmigration from the vascular bed. A similar mechanism exists with the L1 adhesion molecule (L1CAM) as it may specifically bind with αvβ3 integrin present on the endothelial cells. Expression of L1CAM (CD171) was also identified in MCC, however, its role in the metastatic cascade is equivocal as the metastases and recurrences showed lower frequency of expression than primary tumours [42].

The role of the stroma in the development of the neoplasms is being recognized. The constituents of the non-collagenous matrix include fibronectins, tenascin and laminins. Pronounced expression of Tenascin-C at the tumour border in large neoplasms (size > 2 cm) was reported by Koljonen *et al.* [44] and this correlated with malignant behaviour of MCCs.

Cyclin A is a positive regulator of the cell cycle. By phosphorylation of cyclin-dependent kinase 1 and 2 (CDK1, CDK2), it may propel the transition of the cell through S-phase and mitosis [45]. In MCC, expression of cyclin A varied from 5.4% to 69%, with the average of 25%, which is high and in accordance with the aggressiveness of MCC [45]. However, the prognostic value of this marker was not confirmed in MCC, in contrast to that role performed by cyclin A in other malignancies (breast carcinomas, melanoma, etc.).

Prognostic features

The most important prognostic factors in MCC include male sex, larger size of the tumour, involve-

ment of the lymph nodes, small cell morphology, high mitotic rate [17] and absence of lymphocytic infiltration [7].

Data on the phenotypic prognostic factors are less well defined. Fernandez-Figueras *et al*. [37] conducted a study of 43 markers in 31 cases of MCC by means of a tissue microarray technique. The metastatic dissemination correlated with expression levels of matrix metalloproteinase (MMP) 7, MMP10/2, tissue inhibitor of metalloproteinase 3, VEGF, P38, stromal NF-κB, and synaptophysin. Likewise, Ki67 was identified as an important prognostic marker. This protein is involved in the proliferation and is expressed by the cell during the whole cell cycle beyond Go phase. Ki67 labelling index exceeding 50% was correlated with unfavourable prognosis [7]. It is lower in MCC than in SCC and it seems to be an independent prognostic factor associated with the appearance of local recurrences or/and metastasis [25]. The cell cycle regulator proteins e.g. P53, P21, Bcl-2 and Bcl-6 were not shown to have the prognostic value.

Significance of neuroendocrine differentiation for the clinical outcome is not unequivocally confirmed. A higher expression of CD34, synaptophysin, and chromogranin were regarded either as an unfavourable [37] or favourable [44] prognostic factor.

Chromosomal abnormalities

Numerous chromosomal and molecular abnormalities have been reported in MCC. Interestingly, small tumours may have no detectable genomic aberrations even by the comparative genomic hybridization (CGH) technique [46]. Generally, MCC usually presents with overrepresentation of chromosomal material, whereas chromosomal losses appear less frequently. Amplifications are extremely rare in this tumour. Most frequently reported chromosomal gains involve chromosomes 6, 1q, 5p, 1p, 12, 4p, 9, 16p, 19p and 21 in order of frequency as defined by Larramendy *et al.* [46]. Less common chromosomal gains were identified at chromosomal regions: 3p, 3q, 7p, 7q, 8q, 12p, 12q, 13q, 18p, 18q, 19, 20p, 20q, 21q, Xp, Xq, Yp, Yq [19, 24, 47, 48]. Chromosomal losses in MCC affect most frequently chromosome 13q, 4q and 16q in order of frequency [46]. Chromosomal losses at 1p, 2pq, 3p, 4p, 5q, 8p, 10p, 10q, 11 p, 11q, 17p, 17q, Yp, and Yq were reported less commonly [19, 24, 47, 48].

Recurrent high level amplifications were not found in MCC. Those reported sporadically involved chromosomal regions 2p23-24, 4p, 5p, 6p and 13q [46, 47].

Chromosome 1

Alterations of chromosome 1 are frequently reported in MCC and trisomy of chromosome 1 appears to be quite characteristic [19, 24, 49]. Gains of chromosome 1 were detected by different techniques (chromosomal in situ hybridization – CISH, CGH) in 22-37% of MCC [46, 49]. Although its significance is unknown, it seemingly plays a role in conferring the proliferative advantage to the tumour cells [46] as 2/3 of them showed progression to nodal disease. The minimal common region of chromosomal gain occurred at 1q11q31 [46]. Another study indicated another potential region of amplification at 1p34 as it was present in 39% of tumours [24]. This area contains L-Myc (MYCL1) gene locus. This gene has transforming activity and is also amplified in SCC of the lung [50].

Deletions at chromosome 1p36 are quite common in MCC and, interestingly, this alteration is shared by other neoplasms with neural crest derivation, i.e. melanoma and neuroblastoma [47, 51, 52]. Leonard *et al*. [53] detected numerous loci on the short arm of chromosome 1 by means of loss of heterozygosity (LOH) and identified also other deletion sites at chromosome 1p: 1p35 and the centromeric region 1p32-1p33.

Chromosome 6

Gains on both arms of chromosome 6 are one of the most commonly detected chromosomal alterations in MCC [19, 24, 46, 54-57]. Larramendy *et al.* [46] using CGH found overrepresentation of chromosome 6 in 42% (8/19) of studied cases. All of those cases were clinically advanced tumours (size of more than 2cm). Half of them also presented gain of whole **chromosome 12** suggesting that the presence of simultaneous trisomy of chromosome 6 and 12 may play a role in tumorigenesis and progression of MCC [46].

Gancberg *et al.* [55] detected trisomy of chromosome 6 in 47% of cases (8/17) by means of CISH. As the trisomy of chromosome 6 appeared with the same distribution in primary and metastatic tumours, they suggested that this genetic aberration is probably not directly linked with the disease progression. This observation was shared by Vasuri *et al.* [56], who also found trisomy of chromosome 6 not only in cutaneous (6/10 cases) but also in probably primarily lymphonodular lesions (2/4 cases).

By means of fluorescent in situ hybridization (FISH) Suciu *et al*. [54] confirmed these observations as they identified trisomy of chromosome 6 in 85% of MCC cells. These authors suggested the potential contribution of FISH in the diagnosis of MCC with probes for chromosome 6 and chromosome 8 (77% of cells with trisomy of 8).

Several proto-oncogenes located on the long arm of chromosome 6 such as those having kinase activity (PIM-1, ROS-1), transcription factor (MIB), receptors without kinase activity (MAS) [54] or

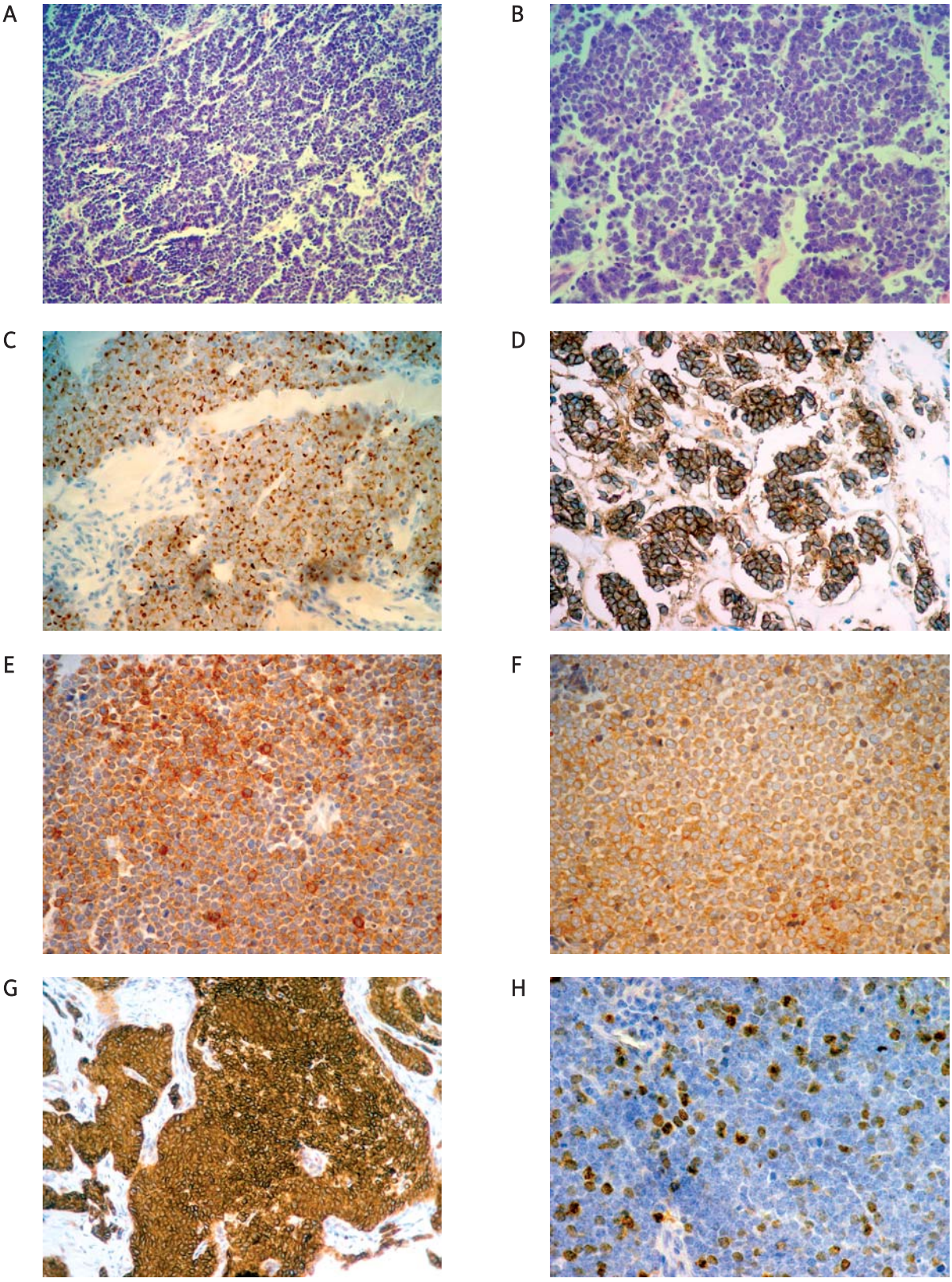

Fig. 1. Merkel cell carcinoma: monomorphous population of "small round blue cell tumor" is arranged in trabecules and garland-like structures (HE, magnification 200×, A). Cytological detailes of the tumor. Note numerous mitotic figures and apoptotic bodies (HE, magnification 400×, B). CK20 positivity shows typical dot-like paranuclear reaction (magnification 400×, C). Neuroendocrine markers CD56/NCAM (D) chromogranin A (E) and synaptophysin (F) shows reactivity in the tumor cells (all magnification 400×). In addition MCC expresses BCL2 (G) and topoisomerase IIα (H) in the cytoplasmic and nuclear location, respectively (magnification 400×). The labeling index of the latter marker amounts to approximately 25%

apoptotic genes BAK1, TNF [48] may potentially play a role in initiation and progression of MCC, but this requires further studies.

Other chromosomal aberrations

Loss of heterozygosity (LOH) was found at **chromosome 3p** [58] and the *FHIT* gene seems to be a potential candidate for the tumour suppressor gene involved in pathogenesis of MCC [19, 24].

Rearrangements on **chromosome 5** are common findings in MCC [19, 24, 46-48]. Gains in **chromosome 5p** were detected in 32% of studied patients [46], whereas deletion at 5q12-21 was revealed in 26% of cases [24].

Loss of heterozygosity at **chromosome 10**q23 was identified in 43% (9/21) of cases [40]. However, the *PTEN* tumour suppressor gene, that has been mapped to 10q23.3, was mutated and homozygously deleted only very uncommonly. This observation does not provide support for a role of the *PTEN* gene in tumorigenesis of MCC.

Chromosome 11q losses are infrequent in MCC, as only 17% of MCCs showed that alteration as defined by CGH [47]. More commonly a deletion of the distal part of the long arm of **chromosome 11** is present in MCC. A detailed study excluded involvement of *SDHD* as a potential tumour suppressor gene candidate in MCC [59].

Karyotypically, Leonard *et al.* [60] found LOH on chromosome 13 in 75% (18 of 24) of studied tumours. The most frequently deleted region was mapped close to the retinoblastoma susceptibility gene (13q14.3) [60]. This observation was confirmed by Paulson *et al.* [24] as they detected deletion of 13q14-21 in 26% of tumours in the region of the RB1 tumour suppressor gene.

Summarizing, it should be emphasized that there is virtually no consistent pattern of chromosomal abnormalities in MCCs. Multiplicity of chromosomal changes in MCC may reflect highly aggressive biology of the tumour and possibly ongoing somatic aberrations during the development of its malignant potential.

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