

A case of Merkel cell carcinoma coexistent with pulmonary small cell carcinoma

Akciğerin küçük hücreli karsinomu ile birlikte olan Merkel hücreli karsinom olgusu

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Merkel cell carcinoma is an uncommon tumor arising usually on the sun-exposed skin of elderly individuals. A 64-year-old male patient, who undergone total laryngectomy operation seven years ago because of squamous cell carcinoma of larynx and got postoperative radiotherapy applied to the hospital with a subcostal mass. Histopathologic examination of the mass revealed tumoral infiltration with cytokeratin-20 expression that forming sheets and solid nests in subcutaneous tissue. The diagnosis was Merkel cell carcinoma. A vegetative tumor located in left main bronchi was observed during synchronously performed bronchoscopy and multiple biopsies were taken. Histopathologic diagnosis was pulmonary small cell carcinoma displaying positive reaction with thyroid transcription factor-1 without cytokeratin-20 expression. It's extremely rare to encounter Merkel cell carcinoma coexisting with pulmonary small cell carcinoma. The current case has special importance due to being an extremely rare encountered tumor besides confirming these markers' reliability in distinguishing Merkel cell carcinoma from pulmonary small cell carcinoma.

Key words: Cytokeratin-20; Merkel cell carcinoma; pulmonary small cell carcinoma; thyroid transcription factor-1.

Merkel hücreli karsinom, çoğunlukla yaşlı bireylerin güneşe maruz kalan derilerinde oluşan nadir bir tümördür. Larenksin skuamöz hücreli karsinomu nedeniyle yedi yıl önce total larenjektomi ameliyatı geçiren ve ameliyat sonrası radyoterapi alan, 64 yaşında erkek hasta subkostal kitle nedeniyle hastaneye başvurdu. Kitlenin histopatolojik incelemesinde, subkutanöz dokuda solid yuvalar ve tabakalar oluşturan, sitokeratin-20 ekspresyonu gösteren tümöral infiltrasyon gözlemlendi. Olgu Merkel hücreli karsinom tanısı aldı. Eş zamanlı yapılan bronkoskopiye sol ana bronшта lokalize vejetatif kitle tespit edildi ve birden çok biyopsi alındı. Histopatolojik tanı sitokeratin-20 ekspresyonu göstermeyen, tiroid transkripsiyon faktör-1 pozitifliği gösteren akciğerin küçük hücreli karsinomu idi. Merkel hücreli karsinom ile akciğerin küçük hücreli karsinomun eş zamanlı birlikte görülmesi oldukça nadirdir. Olgumuz, nadir olma özelliğinin yanı sıra, benzer morfoloji sergileyen bu iki tümörün ayırıcı tanısında kullanılan immünohistokimyasal belirteçlerin güvenilirliğini doğrulaması yönünden önem taşımaktadır.

Anahtar sözcükler: Sitokeratin-20; Merkel hücreli karsinom; akciğerin küçük hücreli karsinomu; tiroid transkripsiyon faktör-1.

Merkel cell carcinoma (MCC) is a rare malignant cutaneous tumor of the elderly characterized by aggressive course with regional nodal involvement, distant metastases and a high rate of recurrence.^[1-5] MCC was first described by Toker in 1972 as trabecular carcinoma of the skin^[3-10] and, since then, has also been called as neuroendocrine

tumor of the skin, Merkel cell tumor, primary small cell carcinoma of the skin, primary undifferentiated carcinoma of the skin, anaplastic carcinoma of the skin or "murky cell" carcinoma.^[3,6-10] MCC and neuroendocrine carcinoma of the skin are the most widely used terms and best reflect postulated origin and immunocytologic characteristics of this

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neoplasm.^[2,6,8] Mainly, squamous cell carcinoma, ovarian and breast carcinoma are secondary neoplasms which accompany MCC with a relatively high incidence.^[2,3,6,11,12]

This tumor is a cutaneous neoplasm that is often hard to diagnose because of its histologic and immunohistochemical similarities to metastatic small cell carcinoma and other cutaneous neoplasms.^[13] We described a case of MCC coexistent with pulmonary small cell carcinoma which also takes place in the differential diagnosis of the same carcinoma. The therapeutic approaches will completely differ whether these two different primary tumors coexist together or one is the metastasis of the other. Because of this, differential diagnosis of these tumors which both have the similar histomorphological characteristics must depend on reliable immunohistochemical markers. The goal of this study is to present an extremely rare case determined as MCC coexistent with pulmonary small cell carcinoma and to stress the importance of immunohistochemical staining for differential diagnosis of these tumors, in the light of literature.

CASE REPORT

A 64-year-old male patient, who had undergone total laryngectomy operation seven years ago because of squamous cell carcinoma of larynx and got postoperative radiotherapy applied to University Hospital with a subcostal mass. During gross examination of the tumor mass that was totally excised; a 3x2x1.5 cm cutaneous and subcutaneous tissue containing a nodule 2.5 cm in diameter was observed. Histopathologic examination revealed tumoral infiltration forming sheets and solid nests in subcutaneous tissue underlying normal epidermis showing continuity in surgical borders (Fig. 1). The tumor was composed of small, round to oval cells of uniform size with vesicular nuclei and multiple small nucleoli. The cytoplasm was scanty and amphophilic and the cell borders were vaguely defined. Mitoses were typically numerous (12/10HPF), and atypical forms were frequently seen (Fig. 2). Apoptosis was marked in the tumor. The immunohistochemical profile was as following: Pankeratin (+), cytokeratin-20 (CK20) (+) (Fig. 3), epithelial membrane antigen (EMA) (+), Ber-EP4 (+), chromogranin-A (+), and synapto-

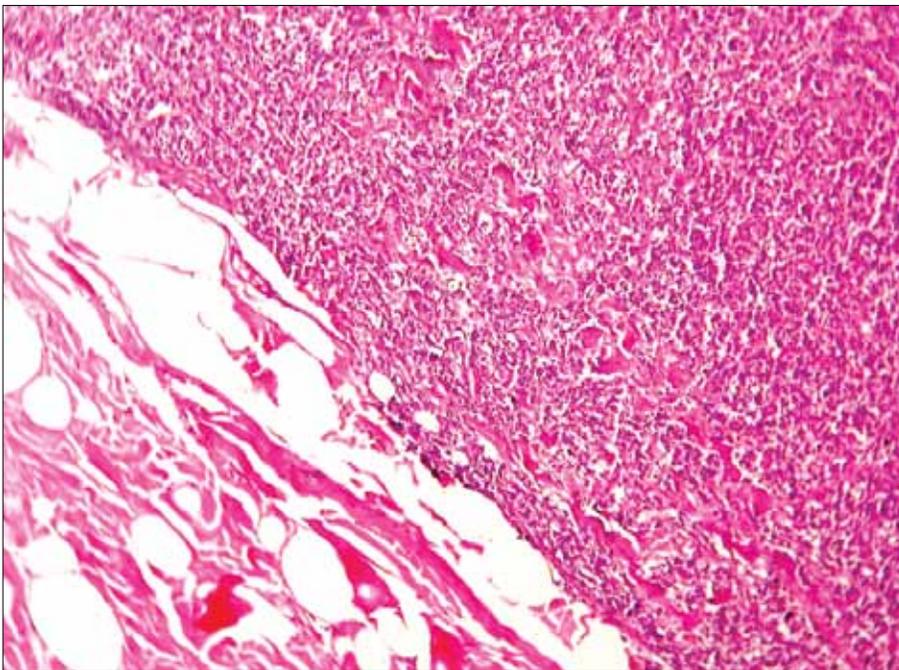


Fig. 1. Solid nests composed of small cells with hyperchromatic nuclei extend throughout the subcutaneous tissue (H-E x 100).

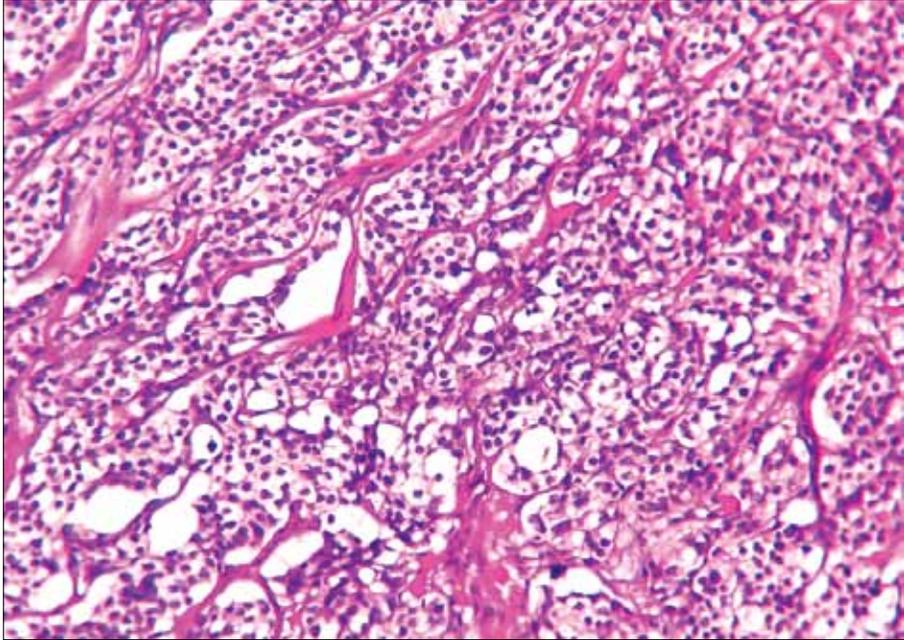


Fig. 2. Sheets of tumour cells with prominent nucleoli and abundant mitoses (H-E x 200).

physin (+). Vimentin, leukocyte common antigen (LCA), cytokeratin-7 (CK7), S-100 protein and HMB-45 were not expressed in the tumor. In the light of these findings the diagnosis was reported as MCC. An additional mass lesion, located in the

apical lateral segment of the left lung, 100x70 mm in dimensions, with soft tissue density was regarded in thorax computerized tomography. A vegetative tumor located in left main bronchi was observed in bronchoscope and biopsy was taken from the

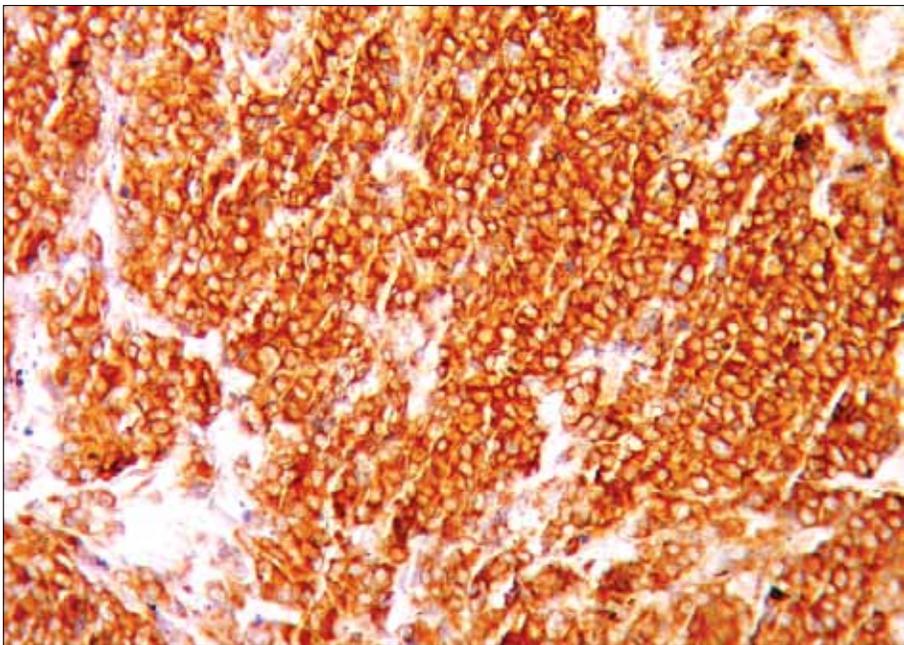


Fig. 3. Immunohistochemical reaction with cytokeratin-20 in Merkel cell carcinoma (B-SA, DAB, x 200).

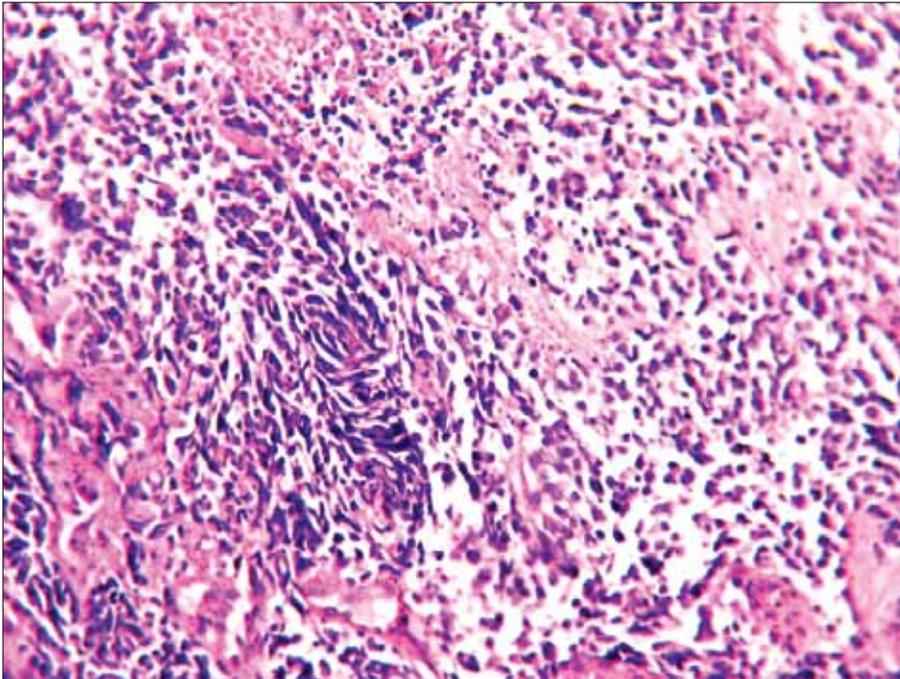


Fig. 4. Sheets of small cells with hyperchromatic nuclei and multiple small nucleoli and tumor necrosis (pulmonary small cell carcinoma) (H-E x 200).

mass. Histopathologic examination revealed pulmonary small cell carcinoma with necrosis (Fig. 4) in which CK20, vimentin, S-100 protein, HMB-45 and LCA were not expressed whereas pankeratin, CK7, chromogranin-A, synaptophysin, EMA, and Ber-EP4 positively reacted. After initial diagnosis, the patient died during further evaluation for staging and therapeutic approaches.

CONCLUSION

MCC is an unusual primary small-cell carcinoma of the skin. MCC is mostly encountered as a solitary nodule and usually arises on the sun-exposed skin of elderly individuals such as head and neck region and upper extremities.^[1-10,14-19] The average age of presentation is 69 years, and only 5% of cases occur before age 50.^[7,9] MCC is encountered primarily in white individuals with equal distribution between men and women.^[5-7] Tumors localized on trunk as in our case have poor prognosis, like localized on hip and thigh. Multiple lesions have been observed; either localized to one region or widely dispersed on the body.^[1,9] The tumor is usually presented as rapidly growing, red to violaceous firm nodule that is less than 2 cm in diameter.^[11,12] MCC

involves the dermis and frequently extends into the subcutaneous fat tissue,^[3-9] only rare cases demonstrates an intraepidermal component.^[3,8,9,17]

Three histological subtypes of MCC have been reported: intermediate, small-cell and trabecular, but these variants have no clinical relevance. Intermediate variant is the most common subtype; the small-cell variant is histologically similar to other small-cell carcinomas and should be distinguished from the bronchial small-cell carcinomas.^[3,6,13] Many histological variants of MCC have been described in the literature by Plaza et al. The tumor can be associated with variety of cytologic appearances, morphologic growth patterns, stromal changes, and other unusual features such as foci of aberrant or heterologous differentiation.^[7]

The origin of MCC is thought to be neuroendocrine cells presented in the basal layer of the epidermis and follicular epithelium and called Merkel cells. However, the exact origin is controversial since immunohistological examination of MCC reveals both epidermal and neuroendocrine features.^[3,10,16,17] Nearly 50% of MCCs exhibit trisomy 6 and distal deletion involving chromosome 1p35-36

is also quite common. Other chromosomes implicated include 18q and 20.^[2]

A significant percentage of patients with MCC are at risk of developing other types of epithelial neoplasms, mainly squamous cell carcinoma, ovarian and breast carcinoma, and sweat gland tumors. Hematologic neoplasms such as Hodgkin lymphoma, B-cell lymphoma, and chronic lymphocytic leukemia have also been associated with MCC.^[3,6,7,20] Co-malignancies, whether diagnosed before, after or simultaneously with MCC, are associated with higher MCC-specific mortality.^[3] We described a case of MCC coexistent with pulmonary small cell carcinoma, which formerly had different diagnosis as laryngeal squamous cell carcinoma.

Usually, MCC can easily be diagnosed by histological examination, but sometimes there may be some difficulties in differential diagnosis due to its similarities with other small cell tumors. These tumors include metastatic oat cell carcinoma, metastatic carcinoid tumor, neuroblastoma, and some types of melanoma, lymphoma and squamous cell carcinoma. MCC can be definitively diagnosed with hematoxylin-eosin and immunohistochemical staining, electron microscopy or both. Immunohistochemical staining can distinguish MCC from these tumors.^[1-10] MCC express both neuroendocrine (neuron-specific enolase, synaptophysin, chromogranin) and CK markers (CK20, CAM 5.2) and is negative for S100 protein and LCA, we determined the similar findings in our case. EMA and Ber-EP4 may also be expressed in MCC and these markers are expressed in our case.^[1-8,15,21] CK7, which identifies bronchial small-cell carcinoma, is negative in MCC.^[1-3,6,7,20] Neurofilament protein is commonly expressed in MCC and often not in bronchial small-cell carcinoma.^[1,2,6]

CK20 which is a low-molecular-weight cytokeratin, is expressed in the gastrointestinal epithelium, urothelium, and Merkel cell.^[3,13] CK20 is also a sensitive and specific marker for MCC and is helpful in differential diagnosis of MCC and pulmonary small cell carcinoma, and other malignant and benign neoplasms of skin.^[2,3,15,16,22] Recent studies suggest that MCCs are consistently CK20

positive. The current case confirms this marker's reliability in distinguishing MCC from pulmonary small cell carcinoma.

Tissue-specific transcription factors control cell determination and differentiation. Thyroid transcription factor-1 is a tissue specific transcription factor expressed in epithelial cells of the thyroid and lung, as well as in certain areas of the brain. TTF-1 is employed to differentiate between MCC and small-cell tumors. TTF-1 is expressed in bronchial small-cell carcinoma and is negative in MCC. Combining TTF-1 with CK20 provides a sound basis for diagnosis.^[1-3,6,18] Early diagnosis is critical, because this lesion has a high rate of local recurrence and metastatic spread.^[21] The best outcome is achieved with multidisciplinary management. We have not encountered a case owing these two tumors coexisting in the same patient in the literature.

We described a case of MCC coexistent with pulmonary small cell carcinoma which also takes place in the differential diagnosis of the same carcinoma. MCC include chromosomes implicated a feature shared with other neoplasms of neural crest derivation. Further new investigations about the probable origins of differentiation of these two tumors may clarify their etiology.

In differential diagnosis of MCC and pulmonary small cell carcinoma an immunohistochemical staining including CK20 and TTF-1 which the reliabilities are confirmed must be used.

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