TTF-1 (Clone SPT24) and CD 99 Positivity in Glioblastoma: A Diagnostic Dilemma

Glioblastomda TTF-1 (Klon SPT24) ve CD 99 Pozitifliği: Tanısal İkilem

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ABSTRACT

We describe an unusual variant of glioblastoma with small cell morphology and discuss its remarkable immunoprofile. Glioblastoma multiforme comprises a morphologically highly heterogeneous neoplasm. However, this heterogeneous immunoprofile of glioblastoma can lead to confusion in the differential diagnosis. A 64-year-old male presented to our hospital. A temporal mass was detected on magnetic resonance examination and surgery was performed. The tumor was composed of a monomorphic collection of densely packed and mitotically active small astrocytes. Proliferated microvessels and palisading necrosis were seen in tumoral areas. Immunohistochemical analysis revealed that the tumor cells expressed GFAP, CD56, NSE, CD99 and TTF-1 (clone SPT24) but there was no expression of clone 8G7G3/1 of TTF-1. TTF-1 expression in glioblastomas cannot rule out primary tumor of the central nervous system even when there is diffuse and strong staining. The clinical and histopathological parameters should be evaluated together for the diagnosis.

Key Words: Brain tumor, Small cell morphology, Immunohistochemistry, Histopathology, Differential diagnosis

ÖZ

Nadir bir varyant olan küçük hücre morfolojisine sahip glioblastom olgusunu dikkat çekici immünoprofili ile tanımladık. Glioblastoma multiforme morfolojik olarak oldukça heterojen bir gruptur. Bununla birlikte, glioblastom heterojen profili ayırıcı tanıda karışıklığa yol açabilir. 64 yaşında erkek hasta hastanemize başvurdu, magnetik rezonans incelemede temporal kitle tespit edildi ve cerrahi uygulandı. Tümör monomorfik sıkışık gruplar yapan, mitotik olarak aktif küçük astrositlerden oluşmaktaydı. Tümöral alanlarda prolifere küçük damarlar, palizatlanan nekroz izlendi. İmmünohistokimyasal analiz yapıldı, tümör hücreleri GFAP, CD56, NSE, CD99 VE TTF-1 (klon SPT24) ekprese ederken TTF-1, klon 8G7G3/1 ile ekspresyon izlenmedi. Glioblastomlarda TTF-1 ekspresyonu diffüz ve güçlü olsa bile santral sinir sisteminin primer tümörünü dışlayamaz. Tanı için klinik ve histopatolojik parametrelerin birlikte değerlendirilmesi gerekmektedir.

Anahtar Sözcükler: Beyin tümörü, Küçük hücre morfolojisi, İmmunohistokimya, Histopatoloji, Ayırıcı tanı

INTRODUCTION

Diffuse infiltrating gliomas are the most common adult malignant brain tumor, accounting for 40% of all primary and 78% of all malignant central nervous system tumors (1). Grade III-IV gliomas constitute about 80% of these tumors (2). Glioblastoma multiforme (GBM) is the most common and the most aggressive primary brain tumor of adults (3).

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GBM comprises a morphologically highly heterogeneous neoplasm and this is the reason it is called "multiforme". Three GBM variants are recognized in the *"WHO classification of tumours of the central nervous system"* (4). However other variants of this entity with histomorphological differences have been described in the literature. These rare variants of GBM include small cell variant, and GBM with oligodendroglial features and primitive neuroectodermal features (PNET-like). Immunohistochemistry can help in the diagnosis of rare variants. the However, heterogeneous immunoprofile of GBM can lead to confusion. At this point, histopathological examination and clinical data should be based for the diagnosis.

We describe an unusual variant of GBM with small cell morphology and discuss the remarkable immunoprofile.

CASE REPORT

A 64-year-old male applied to Antalya Training and Research Hospital with symptoms of headache, imbalance and nausea. On magnetic resonance (MR) examination, a temporal mass was detected on the right side and surgery was performed for tumor excision.

Morphological Examination: A highly cellular tumoral lesion that infiltrated the brain parenchyma was found. In large areas, the tumor was composed of a monomorphic, monotonous collection of densely packed and mitotically active astrocytes with small, uniform, oval-elongated hyperchromatic nuclei. Tumor vasculature consisted of "glomeruloid", complex, proliferated microvessels. In addition, zones of coagulative necrosis lined by "palisading" tumor cells were detected (palisading necrosis).

Immunohistochemical analysis was performed for the tumoral areas. The majority of tumor cells expressed GFAP, CD56, NSE, CD99 and TTF-1 (clone SPT24) but there was no TTF-1 (clone 8G7G3/1), Pan-CK, or Synaptophysin expression. The Ki-67 proliferation index in tumor cells was calculated as approximately 50%.

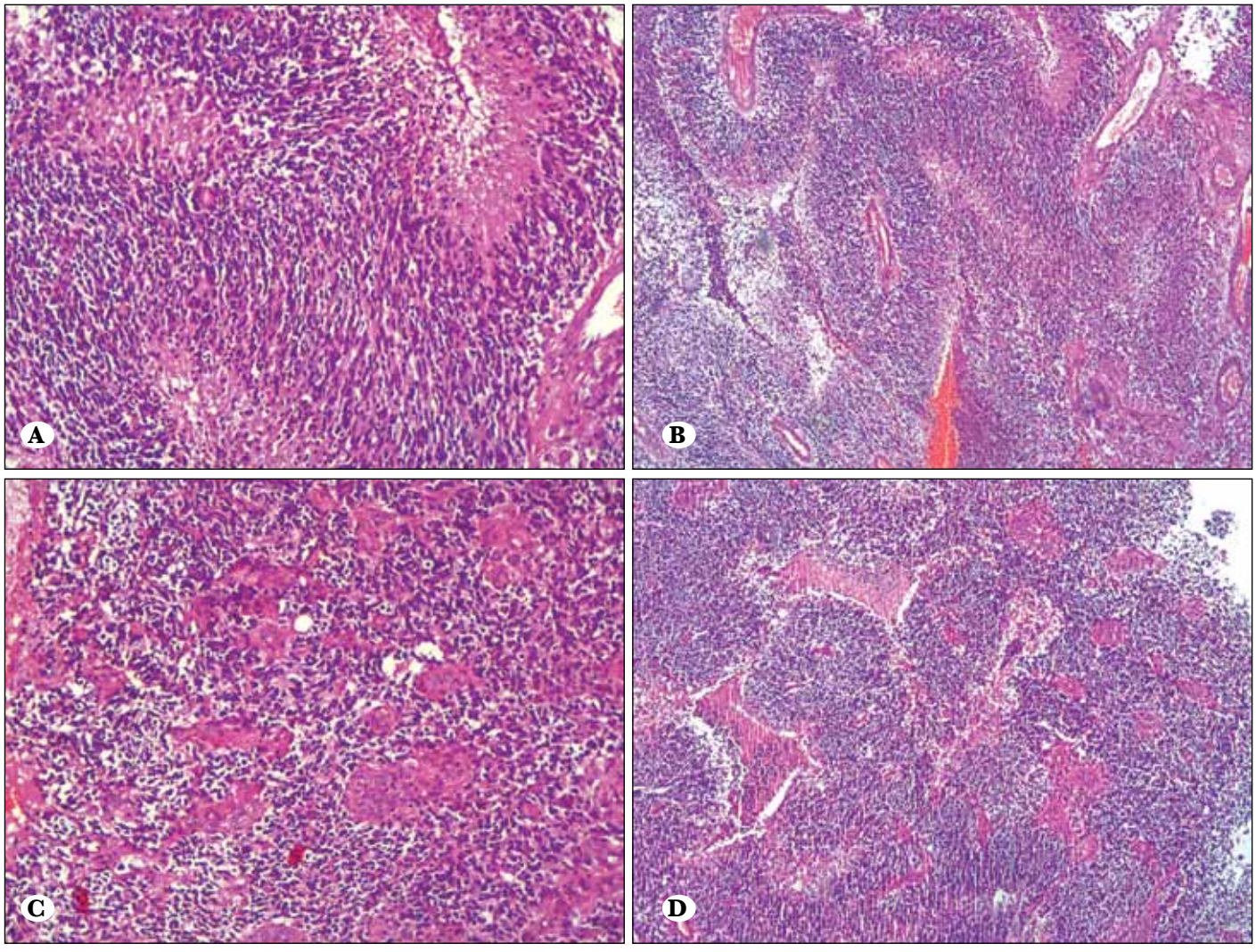

Figure 1: Hematoxylin&Eosin staining **A, B)** Coagulative necrosis lined by "palisading" tumor cells. **C, D)** Tumor vasculature consisted of "glomeruloid", complex, proliferated microvessels.

According to the histopathological findings, and particularly the small cell morphology, palisading necrosis and microvascular proliferation in addition to GFAP positivity in the tumor cells, we diagnosed the tumor as "glioblastoma, small cell variant".

DISCUSSION

Glioblastomas is the most common primary intracranial neoplasm, and is a variable entity with histomorphological and immunohistochemical diversity (2). Three GBM variants were recognized in WHO classification: conventional GBM, giant cell GBM and gliosarcoma. In addition other rare variants were described: small cell variant, GBM with oligodendroglial features and PNET-like features. Small cell variant of GBM is characterized by a population of 80% monotonous, cytologically bland, round or elongated cells with indistinct cytoplasm and high mitotic activity. Immunohistochemistry is an useful method to differentiate GBM from other brain tumors and metastasis. TTF-1 is widely used as an immunohistochemical marker of lung and thyroid tumors. However TTF-1 expression has been described in other tumors such as colorectal carcinoma, gynecological tumors, urothelial carcinoma, prostate, stomach and primary central nervous system tumors (5-8). To our knowledge, there are only 5 studies on the expression of TTF-1 in primary brain tumors (5,6,9-11). Currently two antibody clones are widely used for TTF-1 demonstration: SPT24 and 8G7G3/1. Many studies have demonstrated that clone SPT24 is more sensitive but less specific (12-14).

CD99 is a cell surface antigen expressed in some tumors, particularly Ewing's sarcoma/PNET (15,16). CD99 expression in brain tumors was reported in ependymomas (17). Ishizawa et al. (18) described CD99 immunoreactivity in ependymomas, astrocytomas and reactive astrocytes around the tumor, but brain tumors with clear cell morphology were negative for CD99.

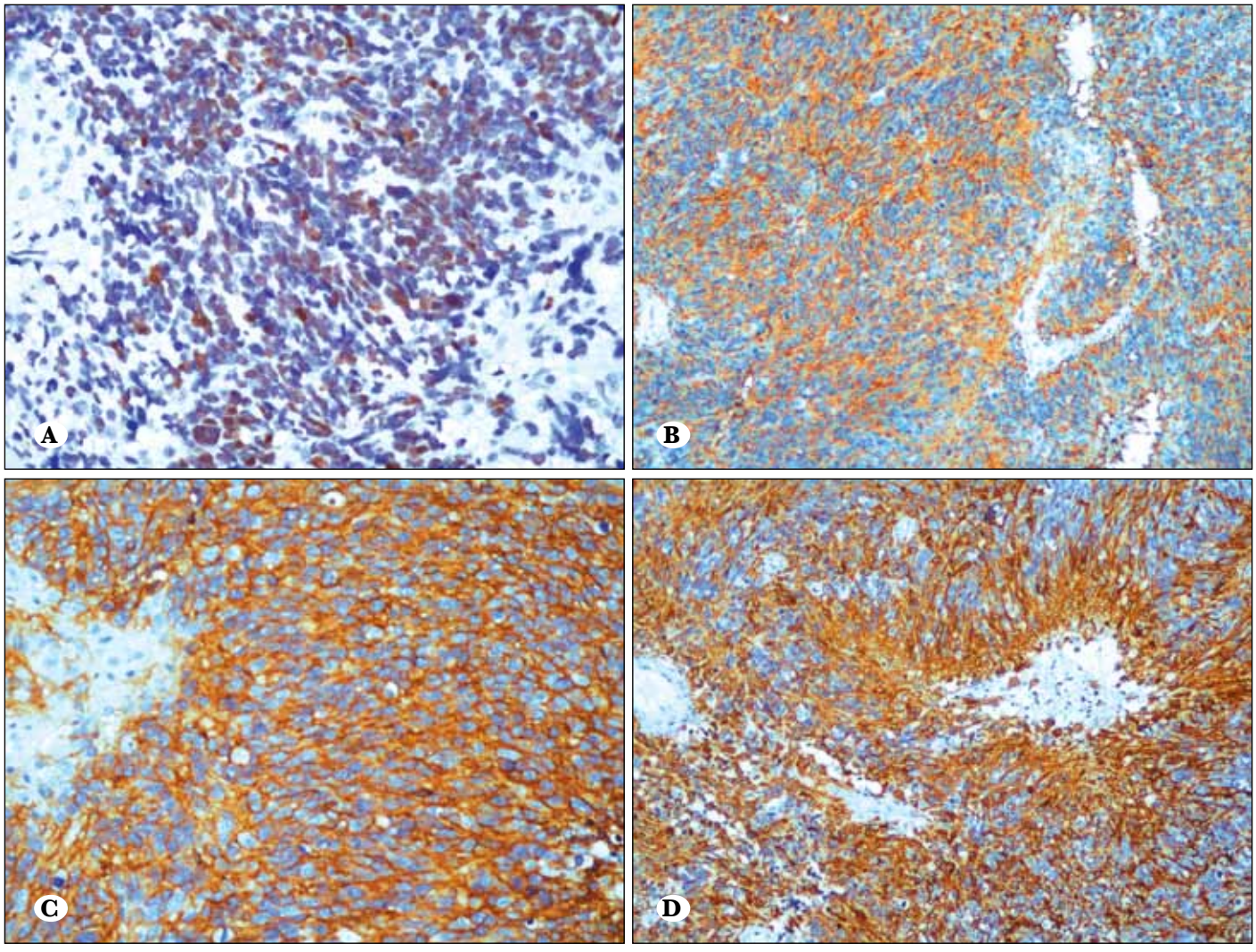

Figure 2: Immunohistochemistry showed the heterogeneity of GBM. **A)** TTF-1, clone SPT24 nuclear positivity in tumor cells, **B)** CD99 immunoreactivity, **C)** CD56 immunoreactivity, **D)** The majority of tumor cells expressed GFAP.

Small cell variant GBM should be distinguished from brain metastasis of small cell lung carcinoma. Therefore, clinical examination, histomorphological features of tumor and immunohistochemical analysis should be evaluated together. In our case, a primary tumor in lungs or in other sites of patient was not detected on MR examination. Histological overview of the tumor was typical for GBM, small cell variant. In addition, immunohistochemistry showed the heterogeneity of GBM as TTF-1 clone SPT24, CD99, CD56, NSE were positive. Diffuse and strong expression of GFAP, palisading necrosis, and microvascular proliferation confirmed the GBM diagnosis. The monotonous small cell population with hyperchromasia in large areas indicated a diagnosis of "small cell variant". TTF-1 expression in GBMs cannot rule out a primary tumor even when there is diffuse and strong staining. The clinical and histopathological parameters should be considered for the diagnosis.

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