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Primary Intracerebral Malignant Lymphoma and Prostate Adenocancer: Cytogenetic Study of a Case

Primer İntraserebral Malign Lenfoma ve Prostat Adenokanser: Bir Olgunun Sitogenetik Çalışması

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ABSTRACT

Primary central nervous system lymphomas are rare tumors that account for less than 2% of primary intracerebral neoplasms. A 70-year-old male who had been operated for prostatic adenocarcinoma ten months ago was admitted with the complaint of amnesia, confusion, stupor and difficulty in walking. Magnetic resonance imaging revealed three mass lesions located in the right anterior temporal lobe, at the mesencephalon left cerebral peduncle and at the right frontal cortex. He was operated and the mass lesion at the right anterior temporal lobe was totally excised. Histopathological examination revealed malignant lymphoma of B cell origin. He was given chemotherapy and radiotherapy. Cytogenetic studies were performed on tissue sections obtained from brain lymphoma and prostate tissues of the patient in order to investigate whether a common genetic abnormality had caused both pathologies. The 1p36 and 22qter regions were studied by fluorescent in situ hybridization analyses in order to detect rearrangements of the regions. 1p36 deletion was detected in the prostate cancer tissue sections of the patient. In the brain tissue specimens, there were normal signals after hybridization with the 1p36 probe and deletion in the 22qter region after hybridization with the 22qter probe. We concluded that these two types of tumors had developed independently.

KEY WORDS: Cytogenetic, fluorescent in situ hybridization, primary intracerebral lymphoma, prostate adenocancer

ÖZ

Primer santral sinir sistemi lenfomaları, primer santral sinir sistemi neoplazilerinin %2'sinden azını oluşturan nadir tümörlerdir. 10 ay önce prostatik adenokarsinom nedeniyle opere edilmiş olan 70 yaşındaki erkek hasta hafıza kaybı, konfüzyon, uyku hali ve yürüme güçlüğü nedeniyle başvurdu. Manyetik rezonans incelemesi sağ anterior temporal lobda, mezensefalon sol serebral pedinkülde ve sağ frontal kortekste üç adet kitle lezyonu olduğunu gösterdi. Hasta ameliyat edilerek sağ anterior temporal lobdaki kitlesi total çıkartıldı. Histopatolojik incelemesi B-hücre kökenli malign lenfoma olarak geldi. Hasta kemoterapi ve radyoterapiyle tedavi edildi. Hastanın beyin lenfoma ve prostat dokularından elde edilen kesitlere her iki patolojinin de ortak bir genetik anomaliden mi kaynaklandığının araştırılması için sitogenetik çalışmalar yapıldı. 1p36 ve 22qter bölgeleri yeniden dizilimlerin araştırılması amacıyla, floresan in situ hibridizasyon analizleriyle çalışıldı. Hastanın prostat kanser doku kesitlerinde 1p36 delesyonu tespit edildi. Beyin doku örneklerinde 1p36 probuyla hibridizasyon sonrasında normal sinyaller elde edildi ve 22qter probu ile hibridizasyon sonrasında 22qter bölgesinde delesyon tespit edildi. Sonuç olarak bu iki çeşit tümörün birbirlerinden bağımsız olarak geliştiğine karar verildi.

ANAHTAR SÖZCÜKLER: Floresan in situ hibridizasyon, primer intraserebral lenfoma, prostat adenokanser, sitogenetik

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INTRODUCTION

Primary central nervous system (CNS) lymphomas are uncommon tumors of the CNS that account for less than 2% of primary cerebral neoplasms and 0.7 to 1.7% of malignant non-Hodgkin's lymphomas (3). In the past decade the incidence of primary CNS lymphomas increased both in high-risk groups (the immunocompromised, AIDS) and in the general population (22).

Prostate cancer is one of the most common human cancers and although familial clustering exists, the majority of cases are sporadic (7). Evidence for a prostate cancer susceptibility locus at chromosome region 1p36 has been determined by linkage studies in high-risk prostate cancer families with at least in one member with primary brain cancer (12).

In the current case we studied 1p36 and 22qter regions by fluorescent in situ hybridization (FISH) analyses in order to detect rearrangements of the regions.

CASE REPORT

A 70-year-old right-handed male was admitted because of amnesia, confusion, stupor and difficulty in walking. His general physical examination was within normal limits and his neurological examination revealed left hemiparesis. His medical history revealed hypertension, hypothyroidism, surgery for lumbar disc herniation and radical retropubic prostatectomy because of prostatic adenocarcinoma 10 months ago. He had received radiotherapy at 5000cGy for the pelvic region and 2000cGy for the prostatic region. His cerebral Magnetic Resonance Imaging (MRI) revealed a mass lesion of 36x36x30mm dimensions at the right anterior temporal lobe. Another mass 10mm in diameter was detected at the mesencephalon and one 7 mm in diameter at the frontal cortex. These mass lesions were isointense with the brain parenchyma in T1A MRI sequences and enhanced heterogenously with intravenous contrast injection. Edema around the lesions were evident in T2A MRI sequences (Figure1).

As the patient had more than one cerebral mass and had been operated on for prostatic adenocarcinoma it was thought that these lesions could be cerebral metastases of prostatic adenocarcinoma. Whole body bone scintigraphy and thoracic and abdominal computerized tomography were performed in order to detect other possible metastatic lesions. The results of these investigations were normal.

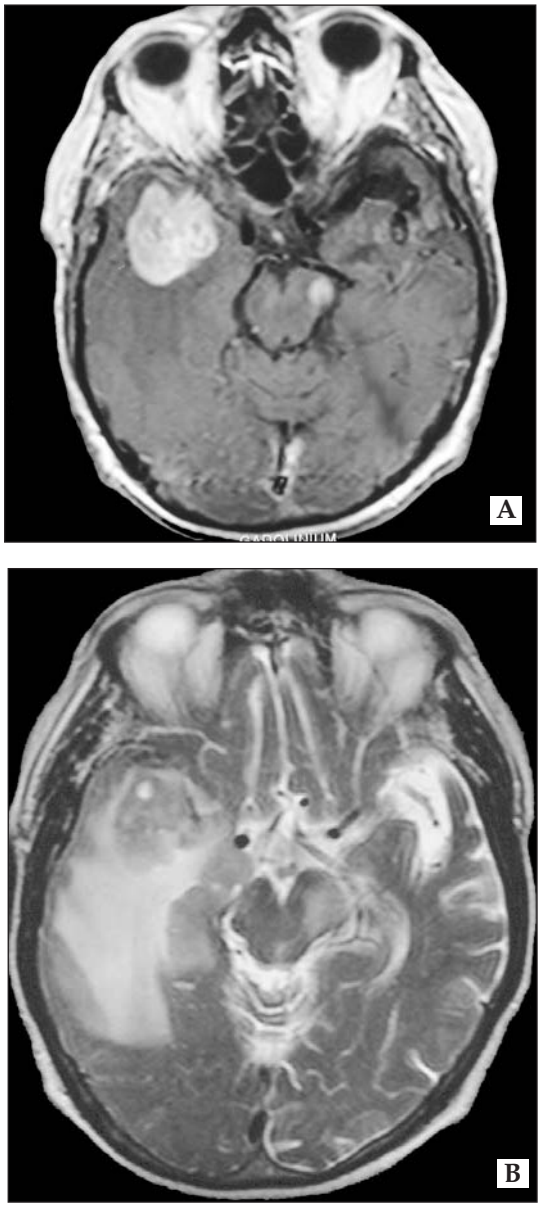


Figure 1: Axial T1 Magnetic Resonance Imaging (MRI) with contrast enhancement
A. Two mass lesions at the right anterior temporal lobe and at the left cerebral peduncle (dimensions of 36x36x30mm and 10mm in diameter respectively).
B. Edema around the lesions were evident in T2 Axial MRI sequences.

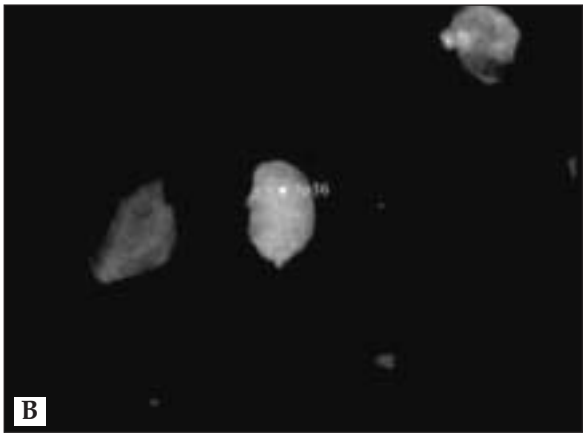
A right temporal craniotomy was performed and a yellowish hemorrhagic soft tumor was totally removed. Histopathological examination revealed malignant lymphoma of B cell origin. After histopathological diagnosis of lymphoma in cerebral tissue, bone marrow biopsy was performed in order to confirm whether the lymphoma was primary or secondary. No disease was detected outside the CNS

and the patient was diagnosed as primary CNS lymphoma. He was given 7000 mgr methotrexate intravenously at the second postoperative week. Radiotherapy at a total of 4600 cGy was also applied to whole cranium in addition to chemotherapy. The MRI three months after radiotherapy was completely normal.

Interphase FISH was performed on 3-mm thick paraffin-embedded tissue sections obtained from brain lymphoma and prostate tissues of the patient. The tissue sections were placed on poly-L-Lysine coated slides and deparaffinized with a slightly modified procedure from that previously described (19). After deparaffinization at 56ºC overnight, xylene dehydration in alcohol, pepsin digestion and fixation of slides, denaturation and hybridization were carried out according to the manufacturer's information for each probe in the HyBrite denaturation/hybridization system for FISH (Vysis Inc., IL).

To investigate chromosome 1 and 22, chromosome 1p36 midisatellit probe spectrum green (Q-BIOgene) and chromosome 22qter spectrum red (Q-BIOgene ptel 22q-R) telomere-specific DNA probes were used respectively. Signals were counted in at least 200 cells for both 1p36 and 22qter by recommended filters (Nikon E600, Kingston, UK).

We detected 1p36 deletion in the prostate cancer tissue sections of the patient (Figure 2). In the brain tissue specimens, there were normal signals after hybridization with the 1p36 probe and deletion in the 22qter region after hybridization with the 22qter probe (Figure 3).



B. 1p36 del: Cell with 1p36 deletion from paraffin sections of prostate tissue

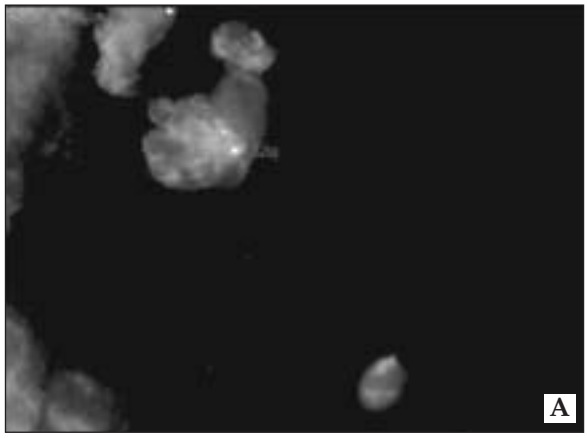


Figure 3: A. 22q N: A normal cell with two signals for 22q.

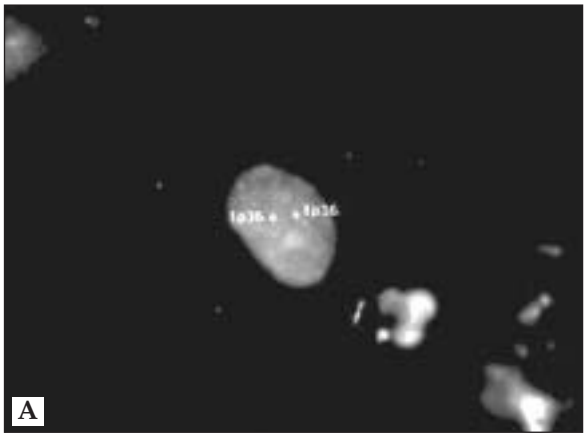
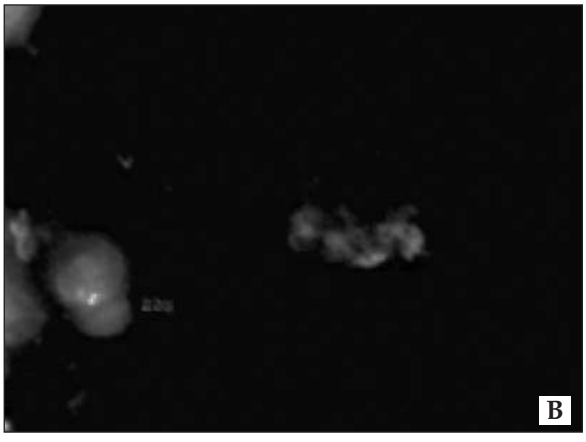


Figure 2: A. 1p36 N: A prostate tissue cell with normal signals for the 1p36 region.



B. 22q del: Cell with 22q deletion from paraffin sections of brain tissue

DISCUSSION

Most intracerebral lymphomas are primary non-Hodgkin's lymphomas. Primary CNS lymphomas are uncommon tumors of the CNS that account for less than 2% of primary cerebral neoplasms and 0.7 to 1.7% of malignant non-Hodgkin's lymhomas (3).

Batallie et. al., reported a series of 248 primary CNS lymphomas consisting of 127 females and 121 males with a mean age of 61. 96.4% were B-cell and 3.6% were T-cell type tumors. There was a single lesion in 66% of the cases, with a supratentorial location in 87%. Tumor location in the basal ganglia, corpus callosum, fornix, infiltration of the periventricular ependyma, or a mirror pattern, were strongly suggestive of a lesion of lymphomatous origin. They determined prognostic factors that were significantly associated with a favorable impact on survival including age younger than 60 years, radiation therapy combined with chemotherapy, and chemotherapy consisting of anthracycline. Partial surgical resection was an unfavorable prognostic factor (3). Tomlinson et al. reported a series of 89 primary CNS lymphomas consisting of 60 males and 29 female with a median age of 60 years. The most common sites for tumor location were frontal, temporoparietal, and basal ganglia and multiple lesions were reported in 23 patients. Of the 66 patients whose phenotype were determined, 63 were B-cell type and 3 were T-cell type. Family history of cancer was present in 33% of patients, three-quarters of whom were first-degree relatives. The median survival time for this study group was 20.9 months. On univariate analysis, prognostic factors significantly associated with survival included age at diagnosis, family history of cancer, and focal neurological deficit (21). In accordance with the findings of the Tomlinson et al. our patient had multiple lesions and the major lesion was located in the temporal lobe.

Several questions remain regarding the optimal management of patients with primary CNS lymphoma. Surgery appears mandatory in most cases to obtain histological diagnosis but does not constitute a therapeutic modality. In contrast to most other brain tumours, debulking or radical surgical excision is not warranted in primary CNS lymphoma, because the lesions are highly infiltrative, often deeply located and likely to respond to chemotherapy and radiotherapy. Partial tumour resection appears to be a negative prognostic factor (3, 10). This has led in recent years to an increased use of stereotaxic needle biopsy in most series (10). For our case we preferred surgical excision of the right temporal mass of the patient instead of stereotaxic biopsy because it was the symptomatic mass, the mass was not deeply located and infiltrative and most importantly we thought it could be the cerebral metastasis of prostatic adenocarcinoma. The success of a stereotaxic biopsy could be low for this patient because he had been given corticosteroids before the operation.

Patients with primary CNS lymphoma commonly show a dramatic clinical improvement after glucocorticoid treatment. In contrast to glial neoplasms and metastases from solid extracerebral tumors, the beneficial effects of glucocorticoids in patients with primary CNS lymphoma are not solely mediated by a reduction of cerebral edema but appear to involve cytotoxic activity. In fact, cerebral mass lesions may resolve completely or incompletely within a few days of glucocorticoid treatment. These patients should not receive glucocorticoids prior to biopsy, but rather receive osmotic agents if increased intracranial pressure necessitates therapy. Inevitably, primary CNS lymphoma recurs despite glucocoticoid treatment, indicating that complete tumor cell eradication is not achieved (26).

Methotrexate therapy has been a mainstay in the treatment of primary CNS lymphoma for years. Although newer studies do not support the additional benefit of intrathecal methotrexate as compared to its venous application, this practice is still continues. High-dose intravenous treatment without intrathecal methotrexate might be more appropriate, in particular, with regard to the possible severe complications (25). Abrey et al. reported use of induction therapy with high-dose methotrexate and cytarabine followed by consolidative high-dose chemotherapy and autologous stem-cell transplantation using the carmustine, etoposide, cytarabine, and melphalan regimen for patients with newly diagnosed primary CNS lymphoma (1).

The median survival time varies between 356 days and 36 months in most clinical series (3, 9, 14, 18, 20, 21, 24). The significant prognostic factors related with survival were age younger than 60 years, Karnofsky performance status, distribution pattern of disease on presenting computerized tomography and radiation therapy combined with chemotherapy. Uncleaved histology, older age,

family history of cancer, focal neurologic deficit, partial tumour resection seem to be unfavorable factors (3, 14, 18, 21).

A prostate cancer susceptibility locus has been reported in families located on the chromosome 1p36 region. Primary brain cancer has been observed in families with a high risk for prostate cancer (12). 1p36 frequently shows loss of heterozygosity in brain tumors and its deletion has been reported in multiple types of brain carcinoma including neuroblastomas (15,16,23), glioblastomas (4), meningiomas (5), oligodendrogliomas (6,13), astrocytomas and mixed oligoastrocytomas (13). Our patient had brain lymphoma that probably explains why we did not detect deletion in the 1p36 region in brain tissue samples. However we observed the deletion in prostate cancer specimens, which supports the study by Gibbs et al. suggesting a prostate cancer susceptibility locus in the region (12).

Badzioch et al. suggest that early onset prostate cancer seems to be associated with the 1p36 region. However, brain tumor association seems to be only change in the families studied by Gibbs et al. (2). Co-occurrence of prostate cancer with other cancers has not been consistent in different studies. Some authors suggest that genetic susceptibility to prostate cancer is site specific only for prostate cancer (17).

We detected 22qter deletion in the brain tissue sections of the patient. 22q region is the most frequent locus involved in brain tumors. Although the tumor did not originate primarily from the brain, the deletion in the 22q region was detected. 22q has been reported to be associated with tumor initiation and oncogenesis in meningioma cases (8, 10, 11). Our finding probably suggests 22qter deletion as a tumor initiation event in tumors involving the brain, regardless of the origin and type of the tumor.

CONCLUSION

The diagnosis of two separate tumors in different organs led us to investigate whether a common genetic abnormality played a role in development of these tumors in the same individual. The results of the genetic examinations described above revealed that prostate carcinoma and primary brain lymphoma developed independently from each other. As cancer is a multi-step process involving a variety of genes, another locus or tumor suppressor gene could have the opportunity to cause the development of different types of tumors in the patient.

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