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Malignant Melanomas Localized to the Parotid Gland

Parotis Bezi Yerleşimli Malign Melanomlar

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Malignant Melanomas Localized to the Parotid Gland

ABSTRACT

Objective: Malignant melanoma situated in the parotid gland represents a rare clinical presentation, and the prognosis of these patients remains inadequately understood in comparison to other forms of malignant melanoma. This study aims to evaluate cases of parotid gland-located malignant melanoma under follow-up in our clinic.

Material and Method: Records of five patients aged 18 and above, diagnosed with melanoma localized within or adjacent to the parotid gland, were retrospectively reviewed. Relevant clinical information such as patients' demographic data including age and gender, medical histories, presenting symptoms, treatment modalities, and outcomes were evaluated. The overall survival of the patients was examined.

Results: None of the patients included in the study had primary parotid gland melanoma. Among all patients, 4 patients had primary lesions that were cutaneous melanomas originating from the head and neck region, while in one patient, the primary lesion was uveal melanoma of the eye. While 3 patients included in the study had died, 2 patients were still being followed up.

Conclusion: Primary melanomas localized to the parotid gland are extremely rare, and when encountered, a thorough medical history and careful physical examination can often reveal that the primary lesion is cutaneous melanoma, predominantly located in the head and neck region. It should be kept in mind that although rare, there may be primary intranodal melanoma cases whose primary is unknown or cannot be found in the parotid gland.

Keywords: Head and neck cancer, melanoma, neoplasms-unknown primary, parotid neoplasms.

ÖZET

Amaç: Parotis bezi içerisinde yer alan malign melanom, nadir bir klinik sunumu temsil eder ve bu hastaların prognozu, diğer malign melanom türleriyle karşılaştırıldığında yeterince anlaşılamamıştır. Bu çalışma, kliniğimizde takip edilen parotis bezi içerisinde bulunan malign melanom vakalarını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Parotis bezi içinde veya komşuluğunda lokalize melanom tanısı alan 18 yaş ve üstü 5 hastanın kayıtları geriye dönük olarak incelendi. Hastaların yaş ve cinsiyet gibi demografik bilgileri, tıbbi geçmişleri, başvuru semptomları, tedavi yöntemleri ve sonuçları gibi ilgili klinik bilgiler gözden geçirildi. Hastaların genel sağkalımları incelendi.

Bulgular: Çalışmaya dahil edilen hastaların hiçbirinde primer parotis bezi melanomu yoktu. Dört hastada primer lezyonlar baş ve boyun bölgesinden kaynaklanan kutanöz melanomlardı, bir hastada ise primer lezyon gözde yer alan üveal melanomdu. Çalışmaya alınan 3 hasta ölmüşken 2 hastanın takibi devam ediyordu.

Sonuç: Parotis bezinde lokalize olan primer melanomlar son derece nadir olup, parotis bezi melanomu ile karşılaşıldığında kapsamlı bir tıbbi öykü ve dikkatli bir fizik muayene ile primer lezyonun ağırlıklı olarak baş boyun bölgesinde yerleşen kutanöz melanom olduğu sıklıkla ortaya konulabilir. Ancak nadir de olsa parotis bezinde primeri bilinmeyen veya primer intranodal melanom vakaları olabileceği akılda tutulmalıdır.

Anahtar Sözcükler: Baş ve boyun kanseri, melanom, primeri bilinmeyen neoplaziler, parotis tümörleri.

Introduction

The most common cause of malignancies in the parotid gland is metastasis to the intra and periparotid lymph nodes (1). The most frequent cancers metastasizing to the parotid gland are squamous cell carcinoma and malignant melanoma (2). Melanoma of the parotid gland is a rare condition and usually develops due to metastasis from primary melanomas originating in the head and neck region (3,4). Although rare, careful examination of the head and neck may reveal regressed cutaneous melanomas when melanoma is observed in the parotid gland.

Due to the scarcity of cases, most studies in the literature have been presented as case reports. In this study, we aimed to discuss cases of parotid gland malignant melanoma treated in our clinic.

Material and Method

All patients diagnosed with malignant melanoma and followed in the oncology clinic of our hospital between January 2015 and January 2022 were retrospectively screened. Data were collected from medical records and the hospital database for patients with melanoma localized in the parotid gland, confirmed histopathologically. Patients' age, gender, primary or metastatic status, the reason for hospital admission, treatments received, last follow-up dates, and status at the last follow-up were recorded. In addition, histopathological examination and immunohistochemical findings were noted after re-evaluation.

Statistical analyses were performed using IBM SPSS Statistical Software (IBM SPSS Statistics version 22.0, IBM SPSS, USA). The clinical and demographic characteristics of the patients were analyzed by descriptive analysis. Categorical and numerical variables were presented as numbers and percentages (n, %). Continuous data were expressed as means ± standard deviation when the data follows normal distribution; otherwise, they were expressed as median and range. Survival outcomes were compared using the Kaplan-Meier method with the log-rank test. The time from the parotid gland metastasis to the last control or the date of death was accepted as overall survival (OS). The ethics committee approval of the study was given by the Ankara Etlik City Hospital ethics committee. (number: AEŞH-EK1- 2023-783, date:10.01.2024)

Results

A total of 5 patients were included in the study. Three (60%) of the patients were male. The median age was 64 (60-82) years. The clinicopathological characteristics of the patients are presented in Table I. No patient had primary parotid melanoma, and none of the patients' primary lesions had regressed spontaneously. In all patients, primary lesions and parotid metastases were pathologically confirmed. While 4 patients had cutaneous melanoma as the primary lesion, one patient had uveal melanoma as the primary lesion. Regarding the location of the primary lesions, one patient had the lesion in the left frontoparietal region, one patient in the left frontotemporal region, one patient on the left side of the neck, one patient under the left eye, and one patient had a primary lesion of the right eye, which was uveal melanoma (Figure I).

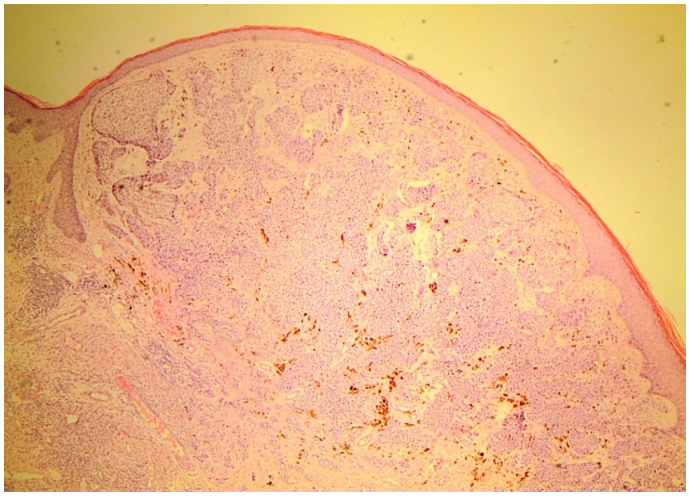

Figure I. Dermal nodular melanocyte nests in frontotemporal skin lesion (Hematoxylin and Eosinx40)

Two patients presented to the hospital due to swelling in the parotid region before the diagnosis, two patients due to lesions on the scalp, and one patient due to vision problems. In three patients, parotid metastasis was present at the time of diagnosis. In one patient, parotid metastasis developed 5 months after the initial diagnosis, and in another patient, it occurred 40 months later. Among the other metastatic sites, lung metastasis was observed in three patients, bone metastasis in three patients, liver metastasis in two patients, and lymph node metastasis in only one patient.

Table I. Clinicopathological characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Male	Female	Female	Male
Age (at diagnosis, years)	60	82	63	77	64
Location of primary tumor	Left Frontal skin	Unknown	Right uveal melanoma	Left cheek skin	Left parietofrontal scalp
Time of parotid gland metastasis	At diagnosis	At diagnosis	40. month after diagnosis	5. month after diagnosis	At diagnosis
Other metastatik sites	Lymph node	Lung	Lung, liver, bone	Liver, bone	Bone
Involved parotid gland	Left	Left	Right	Left	Left
BRAF mutation	Mutant	Wild	Wild	Wild	Mutant
Treatment type	1. Dabrafenib +Trametinib	1. Temozolamid 2.Nivolumab	1. Temozolamid 2. Nivolumab 3. Paclitaxel	1. Temozolamid 2. Nivolumab	1. Temozolamid 2. Nivolumab
OS (months)	18 (Alive)	58 (Died)	37 (Died)	37 (Died)	13(Alive)

BRAF: B-Raf proto-oncogene, OS: Overall Survival

Diagnosis was confirmed through fine needle aspiration cytology (FNAC) of the relevant mass lesion and subsequent immunohistochemical staining of Human Melanoma Black-45 (HMB45), Melan A, S100 (pS100), and/or Sry-related HMg-Box gene 10 protein (SOX10) in the prepared cell blocks.

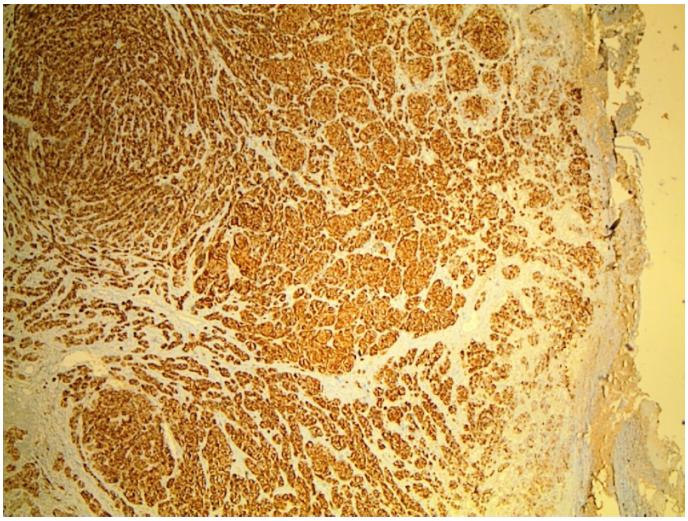

Figure II. Diffuse cytoplasmic HMB45 expression in melanocytes(Immunohistochemistry, HMB45x100)

Two patients with cutaneous primaries were found to have the B-Raf proto-oncogene (BRAF) V600E mutation, which is known to promote the growth and spread of melanoma cells. Treatment regimens were evaluated, and among the patients in the metastatic stage, three received temozolomide, one received Nivolumab, and one received dabrafenib+trametinib combination therapy.

In terms of OS, three patients died at the time of the last follow-up, while two patients were still under observation. The survival durations of the deceased patients were 37 months, 58 months, and 37 months, whereas the remaining patients were being followed up at 13 months and 18 months.

Discussion

Although primary malignant melanomas of the parotid glands are rare, melanomas are the second most common cause of parotid gland metastases (5). The most frequent origin of melanomas that metastasize to the parotid gland is known to be cutaneous melanomas in the head and neck region (4). Rarely, melanoma can be seen in the parotid parenchyma or parotid lymph nodes without a known primary, which may be attributed to regressed cutaneous melanomas or ectopic intranodal nevus cell inclusions (6,7).

Metastases from parotid melanomas are typically presented with swelling in the preauricular region. In these instances, ultrasonography is typically employed as the primary diagnostic tool, while positron emission tomography and computed tomography are often utilized for screening distant metastases. FNAC for diagnostic purposes and immunohistochemical examination of cell blocks serve as both non-invasive

and cost-effective methods.

In a series presented by Prayson et al. comprising 12 cases, the median age was 66 (range: 30-84) (8). Only one case had an unknown primary, and the remaining 11 patients had primaries in the head and neck region. Among these patients, 11 presented with a mass or nodule. The left parotid gland was involved in 5 patients, while the right parotid gland was involved in 6 patients (8). Some case reports have also described parotid metastasis in patients without a known primary, with two of those cases presenting with swelling in the right parotid gland (3,9). In our study, the median age resembled that of the aforementioned study, albeit with a higher incidence of left parotid gland involvement.

The identification and differentiation of lesions in the parotid gland pose a significant clinical challenge, particularly in cases where a malignant history is present. Although the most common tumors metastasizing to the parotid gland are cutaneous squamous cell carcinoma and melanoma (2), distinguishing between benign and malignant lesions, as well as determining whether they are primary or metastatic, remains complex. Given that benign tumors are predominant among parotid gland neoplasms (10), an essential consideration arises in isolating malignancies within parotid masses. While imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging are routinely employed for differential diagnosis, their efficacy may be limited. Consequently, FNAC, core needle biopsy, or excisional biopsy are invaluable for achieving a definitive pathological diagnosis. In our study, excisional biopsies were performed in one patient, while ultrasound-guided core needle biopsies were conducted in four patients.

The gold standard for diagnosing melanoma involves the demonstration of melanin pigment pathologically (11); however, in many instances, the diagnosis relies on the positivity of S100 and HMB45 immunohistochemical stains (12) (Figure II). Confirming the presence of melanin, along with the positive expression of S100 and HMB45 immunohistochemical stains in all our cases, unequivocally confirmed the pathological diagnosis of melanoma metastasis to the parotid gland. Also, the primary tumors in all patients originated from the head and neck region. Overall, patients with parotid metastasis tend to have shorter OS. In Prayson et al.'s series, half of the patients died within 2 years of parotid gland metastasis (8). In Wang et al.'s series of 17 patients, 9 patients died within an average of 2.6 years (13). In our series, after parotid metastasis, the survival durations were 37 months in 2 patients and 58 months in 1 patient, while the other 2 patients were still being followed up at 13 and 18 months after the parotid gland metastasis.

The main treatment for salivary gland malignancies, including melanomas, is generally surgery. Adjuvant radiotherapy may be added based on pathological evaluation after parotidectomy and neck dissection (14). In patients with widespread metastases and BRAF mutations, combination therapies targeting BRAF and Mitogen-activated protein kinase (MEK) inhibitors such as dabrafenib+trametinib, encorafenib+binimetinib, and vemurafenib+cobimetinib are used as targeted treatments (15-17). For patients without mutations, recently approved immunotherapy agents such as nivolumab, ipilimumab, and pembrolizumab are considered the first-line options (18,19). Additionally, alternative treatments such as temozolomide and historically significant interferon therapies are among the options. In our country, the lack of reimbursement for current treatments by the government and the challenges in accessing medications have resulted in none of our patients receiving the first-line standard treatments recommended in recent guidelines. The majority of patients underwent treatment with temozolomide, an older option that has fallen out of favor as a first-line therapy. The possible reason for our patients' overall shorter survival durations, as compared to current literature data, may be attributed to their inability to receive optimal treatment. The financial barriers and limited access to state-of-the-art therapies underscore the pressing need for improved healthcare policies and increased efforts to ensure that patients have equitable access to the latest and most effective treatments.

It is essential to acknowledge several limitations in our study. Firstly, the retrospective, single-center nature of the study introduces the potential for bias. Secondly, the study is constrained by a limited and heterogeneous patient population, thereby restricting the robustness of our findings. Additionally, the

notable limitation lies in the fact that the patients did not receive optimal treatment according to the evolving treatment algorithms in recent years. When interpreting the results of the study, these limitations should be taken into consideration, emphasizing the need for cautious interpretation and generalization of the findings. Future research endeavors should aim to overcome these limitations by incorporating larger, more diverse patient cohorts and adopting prospective study designs to enhance the reliability and applicability of the results.

In conclusion, primary melanomas of the parotid gland are extremely rare. When parotid melanoma is encountered, a thorough medical history and physical examination are essential. This allows for the identification of a primary lesion in many patients, with the most common origin being cutaneous lesions in the head and neck region. Sometimes, a previously excised skin lesion mentioned in the patient's history may serve as a primary lesion without any other lesions present.

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