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Clinical and histopathological analysis of metastatic brain tumours: A single-centre experience

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ABSTRACT

Objective: The aim of this study is to determine the demographic and clinical findings of cases which have been operated for a brain mass and have metastasis, to analyse the histopathological findings, to draw attention to the molecular tests that are effective in the treatment of the primary tumour, and to compare our results with the literature data.

Material and Methods: One hundred seventy cases diagnosed with brain metastasis tumour between January 2012-2021 were analysed retrospectively. The clinical findings and demographic information of the cases were recorded from the hospital information system. The diagnoses of the patients diagnosed with metastasis, the analysis of the cases with or without a primary tumour at the time of diagnosis, and the immunohistochemical staining applied to detect the primary metastasis were recorded.

Results: Sixty-seven of the cases were female, and one hundred three were male. The youngest case was 14, and the oldest case was 90 years old (Mean 55.6 ± 14). While the clinical findings in 35 of the cases were solely headache, 41 patients also had at least one of the symptoms such as dizziness, seizure, weakness, and ataxia in addition to headache. The primary was unknown at the time of diagnosis of brain metastasis in 63 of the cases. There was a single focus in 107 cases, and multiple metastasis focus in 63 patients. Among all cases, lung (84), breast (24) colorectal (15), kidney (9) metastases were the most common. Primary focus could not be detected in 2 of the cases (neuroendocrine carcinoma and adenocarcinoma) despite all imaging techniques as well as immunohistochemical findings.

Conclusion: The possibility of metastasis is also present in cases with a single lesion and whose primary diagnosis is unknown, and histomorphological analysis become inevitable due to the increase in molecular examinations and the development of patient-specific treatment protocols. Besides, it should not be forgotten that the most common tumour-causing brain metastasis -whether or not the primary is known- is the lung. Kidney tumours may also present with metastasis without manifesting themselves.

Keywords: metastasis, brain, pathology, immunohistochemistry

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INTRODUCTION

Brain metastasis is ten times more common in adults than primary tumors of the brain. Frontal lobe and cerebellum are the regions where metastases are detected most frequently. Brain metastasis can be seen in approximately 10-30% of cases with a diagnosis of primary tumor. In cases with brain metastasis, the lifetime suddenly becomes shorter and may be shorter than 2 months on average (**1**). The prognosis of cases with brain metastasis varies according to the location of the primary tumour. Lung cancer can metastasise within an average of 4.5 months after diagnosis, and the breast within 41 months (**2-4**). Tumour species that metastasise to the brain are lung, breast, melanoma, and colorectal tumors in order of frequency (**5, 6**). In cases with a primary diagnosis in any organ, metastasis is considered in the presence of a single or multiple lesions in the brain. However, in cases with no primary tumour diagnosis or with single metastasis, high-grade central nervous system tumours are also included in the differential diagnosis. In the treatment of metastatic brain tumours, chemotherapy, fractionated radiotherapy or whole-brain radiotherapy (WBRT) are among the methods used along with surgery (**6**).

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When metastatic foci is single, they can be removed by surgery or stereotactic surgery; however, surgery cannot be performed since multiple metastases can occur in approximately 80% of the cases (**6, 7**). Increasing molecular studies and initiation of target therapies are significant for some primary tumors and its subtypes such as small cell lung carcinomas, melanoma, breast, and kidney cancers (**2**). Most of the brain metastases are resistant to chemotherapeutics; nevertheless, the systemic effects of the drugs used are utilised. Considering that the lifetime of patients with brain metastasis will be short, diagnosis and determination of the primary organ play a vital role in patient management and treatment in metastasis surgery.

MATERIAL and METHODS

The study included patients who had opere at Bezmialem Vakıf University Faculty of Medicine between January 2012-2021, and who had brain and medulla spinalis metastasis. The clinical findings and demographic information of the cases were recorded from the hospital information system. The diagnoses of the patients diagnosed with metastasis, the analysis of the cases with or without a primary at the time of diagnosis, and the immunohistochemical staining applied to detect the primary metastasis were recorded. The obtained findings were compared with the literature findings.

Statistical Analysis: Data were analysed with IBM SPSS Statistics 22.0 package program. Median, mean standard deviation values, frequency, and percentage values were given as complementary statistics. The study was approved by the Ethics Committee of Bezmialem Vakif University with the approval number 2021/125.

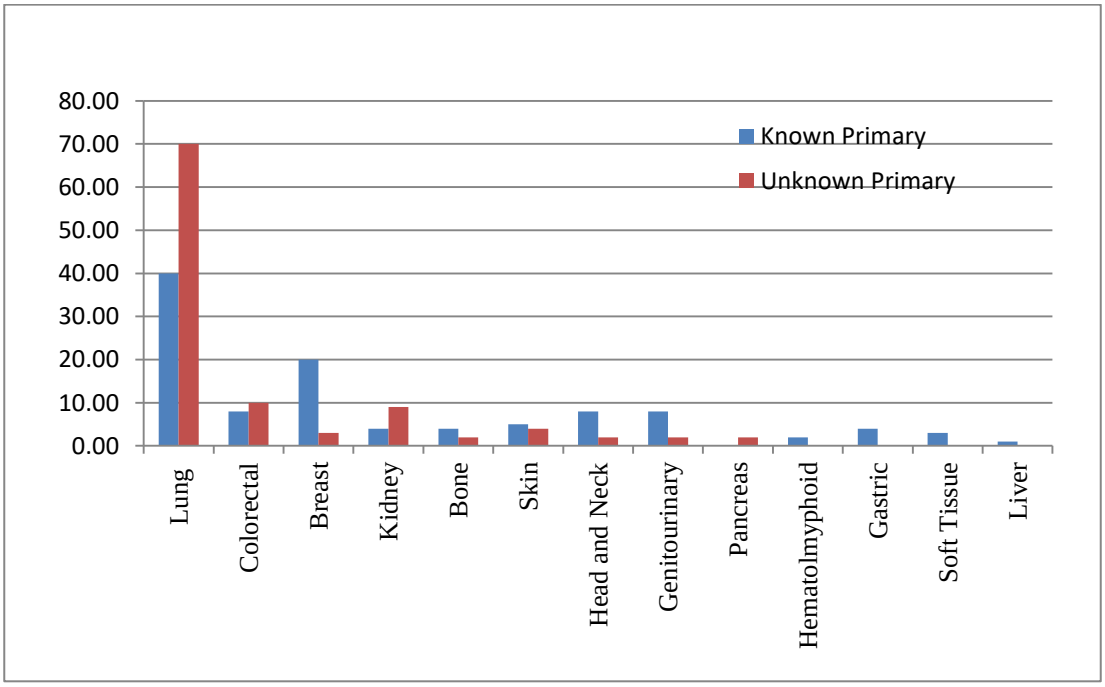
RESULTS

The 67 of 170 cases included in the study were females, and 103 were males. The youngest case was 14, and the oldest patient was 90 years old (Mean 55.6 ± 14).

Whereas the most common location was the cerebellum(45), followed by the frontal (36), medulla spinalis (20), parietal (16), temporal (16), occipital (15) lobes. Metastasis was present in two different lobes in 18 cases, in the sella in 1 case, and in the intraventricular region in 12 patients.

While the clinical findings in 35 of the cases were solely headache, 41 patients also had one of the symptoms such as dizziness, seizure, weakness, and ataxia in addition to headache. Furthermore, weakness, and numbness in the extremities, speech disorder and dysmnesia were other findings. Primary malignancy was not known at the time of diagnosis in 65 brain metastases. There was single focus in 107 cases, and multiple metastasis focus in 63 patients. The diagnosis was adenocarcinoma in 126 (74.1%) of the cases, squamous cell carcinoma in 17 (10%), 11 (6.5%) small cell neuroendocrine carcinoma, 7 (4.1%) cases malignant melanoma, 7(4.1%) cases sarcoma, 2 (1.2%) cases were lymphoma (**Figure 1**). Among all cases, lung (84), breast (24) colorectal (15), kidney (9) metastases were the most common. The primary focus could not be detected in 2 of the cases (neuroendocrine carcinoma and adenocarcinoma) despite all imaging techniques as well as immunohistochemical findings. The mean time elapsed between cases with a definite primary tumour and brain metastasis was 34.6 months, and the latest metastasis (38 years) was thyroid papillary carcinoma metastasis. Thirty-one of the cases were still alive, and 139 died.

When metastatic lesions are found, a graph of tumours with unknown primary and cases with known primary are given in the **Graph 1**. Except for two tumours where the primary focus could not be detected, considering the primary of 63 cases whose primary was unknown during metastasis, Lung was 44 (69.8%), Colon was 6 (9.5%), Kidney was 5 (7.9%), Breast was 2 (3.2%), Skin was 2 (3.2%), Bone was 1 (1.6%), Pancreas was 1 (1.6%, Prostate was 1 (1.6%), and Thyroid was 1 (1.6%).



Graph 1. Table comparing which organ/system tumors originate from primary and unknown primary tumors during the diagnosis of brain metastasis. Values are given as %.

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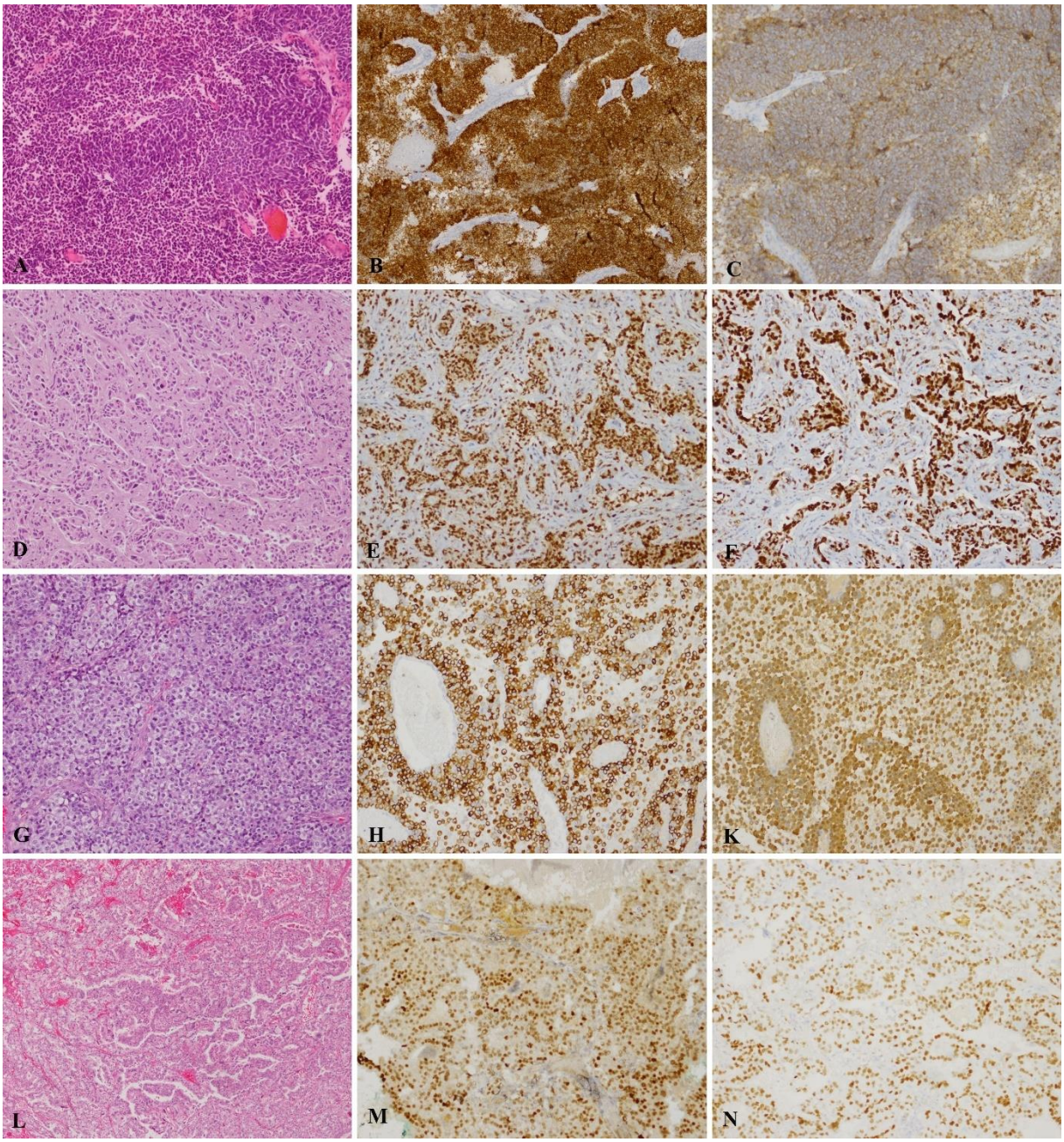

Figure 1. Small cell lung carcinoma (A, H&E), immunohistochemical TTF1 (B) and Synaptophysin staining (C), Breast carcinoma metastasis (D, H&E), immunohistochemical GATA (E) and Estrogen staining (F), Malignant melanoma metastasis (G, H&E) , immunohistochemical Melan A (H) and S100 staining (K), Thyroid papillary carcinoma metastasis (L, H&E), immunohistochemical PAX8 (M) and TTF1 staining (N). Original magnification x100)

DISCUSSION

Metastases are the most common cause of brain tumors in adults and are 10 times more common than primary brain tumors (5). This rate is increasing more with the development of imaging techniques. The most common areas where metastases are seen are the brain, cerebellum, and brain stem, as in our study, and rarely in the choroid plexus and suprasellar localisations. 12 metastases were found in the choroid plexus and 1 in the suprasellar region in our study. Hematogenous spread through arteries is often expected in brain metastases.

Metastases are often occur in the area between the middle cerebral artery and the posterior cerebral artery. In our study, metastases were most frequently seen in the frontal lobe between the middle cerebral artery and anterior cerebral artery, and then in the parietal lobe.

However, the retrograde perineural spread can also be seen, particularly in head and neck tumours (8). The primary of 8 of our cases are head and neck tumours.

In the literature, primary tumour focus includes lung, breast, melanoma, and colorectal tumours in the top four. In our study, lung, breast, colorectal tumours, and kidney metastasis were found in the top four. Contrary to the literature, considering tumours with known and unknown primary during metastasis, in cases with known primary during metastasis, there are lung, breast, colon metastases, respectively; while it was observed that lung, colon, and kidney metastases were more common in cases of unknown primary. Although lung metastasis is in the first place in both groups, it has a rate of 40% in those with a known primary and around 70% in the group with an unknown primary. Among the immunohistochemical markers applied to detect the tumour in the primary unknown group, TTF1, CK7 for lung, CK20, SATB2, CDX2 for colon, RCC, PAX8 for kidney, S100, HMB45, and SOX10 for melanoma are the most widely used. The right panel should be used after the prediction for the primary in the company with morphological findings. Considering that almost 70% of tumours with unknown primary are lungs, we emphasise that it should not be forgotten that lung metastasis should be excluded, and kidney metastases take the third place among those with unknown primary tumours.

The presence of extracranial metastasis determines the patient's condition, the location, number, and diameter of the tumour, and the condition of the primary tumour (**9**). Along with the increase in systemic treatments, the improvement of imaging techniques, and the improvement of supportive therapies, progression-free survival has been observed recently (**10**). However, although the primary focus was detected and treated in some of the patients, there is a group with a short lifetime. This is due to the genetic heterogeneity in the primary tumour and the metastatic tumour (**11**). Particularly the mutations in non-small cell lung carcinoma (NSCLC) and melanoma, and the hormone receptor status in the breast affect the prognosis. Brain metastasis is observed in approximately half of the patients during the course of NSCL carcinoma (**12**). Epidermal growth factor mutation (EGFR), which is seen in 15% of NSCLDs, is particularly associated with adenocarcinoma histology, under 35 years of age, non-smoker, and Asian patients. The presence of an EGFR mutation affects the response to tyrosine kinase inhibitor therapy (**13**). Breast tumours are the other tumour that most frequently metastasises to the brain after NSCLC. In breast tumours, as well as TNM staging and tumour subtype, being younger than 40 years old, presence of lung metastasis and performance status also affect the prognosis. The basal-type brain metastasis development time is relatively short among tumour types, as in the Sperduto et al. study (**14**). Of our 24 breast tumours with brain metastasis, 8 had basal, 9 had luminal B, and 6 had HER2 type, the data of two cases could not be reached, and luminal A was not present. The time between primary tumour diagnosis and metastasis was the shortest in basal type. About half of melanomas, which comprise 10% of brain metastases, particularly in young patients, have BRAF mutation. The presence of BRAF mutation is significant for treatment. However, it is not effective in predicting the development of brain metastasis or increasing the risk (**15**).

CONCLUSIONS

In addition to histomorphological findings, an increase in the variety of molecular examinations and immunohistochemical stainings presents a valuable guide in the distinction of primary metastasis. It should not be forgotten that the most common tumour-causing brain metastasis-whether or not the primary is known- is the lung, and kidney tumours may also present with metastasis without manifesting themselves.

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