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Miliary cerebral metastases: prevalence and radiological findings

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ABSTRACT

Aims: Miliary cerebral metastases, also known as carcinomatosis encephalitis, represent an unusual form of metastatic disease in the brain. Due to their rarity, limited literature is available, restricting our understanding of this condition. This study aimed to evaluate the prevalence and imaging characteristics of miliary cerebral metastases in a cohort of metastatic patients.

Methods: A retrospective review was conducted on approximately 618 contrast-enhanced MRI scans from patients with metastatic disease who had not undergone surgical intervention or received radiotherapy. Cases of miliary cerebral metastases were identified and analyzed. Demographic data, primary cancer types, non-contrast CT and MRI findings of miliary metastasis cases were evaluated.

Results: Miliary cerebral metastases were identified in 6 out of the 618 metastatic patients included in the study. The radiological features included small, disseminated hyperintense lesions visible on post-contrast T1-weighted images. These lesions were diffusely scattered throughout the brain, predominantly at the grey-white matter junction.

Conclusion: Our findings highlight the rarity of miliary cerebral metastases, supporting the limited cases reported in the literature. These findings underscore the need for increased clinical awareness and further research into this condition. High-resolution, contrast-enhanced MRI plays a vital role in detecting and characterizing miliary cerebral metastases, aiding in their management.

Keywords: Miliary cerebral metastases, carcinomatosis encephalitis, metastatic disease, MRI, brain metastases

INTRODUCTION

Miliary cerebral metastases, or carcinomatous encephalitis, is a rare but severe form of brain metastatic disease.[1,2] This condition, characterized by numerous small, disseminated lesions spread throughout the brain, mimics the miliary spread in certain infectious diseases such as tuberculosis.[1,3] However, these disseminated lesions in the context of brain metastases originate from various primary cancers, including but not limited to breast, lung, and gastrointestinal tumors.[4-9]

Despite the significant burden that brain metastases impose on patients' quality of life and survival, the unique subset of miliary cerebral metastases remains poorly understood.[10,11] The exact incidence of miliary cerebral metastases is uncertain, primarily due to its rarity, and it is thought to represent only a small fraction of all brain metastases. The clinical presentation can often mimic infectious diseases, leading to potential misdiagnosis, delayed treatment, and adversely impacting patient outcomes.[8,12-14]

Furthermore, the treatment and prognosis of patients with miliary cerebral metastases are areas of ongoing research. The response to various treatments varies, including targeted therapies and radiotherapy, and survival outcomes are generally poor.[5,11,18,19] Unfortunately, the existing literature primarily consists of case reports and small case series, limiting our understanding of this complex condition.[1,3-7,12-16,19-22]

Given the diagnostic complexity, potentially severe clinical implications, and the lack of robust, high-quality data, this study aims to provide a more comprehensive understanding of miliary cerebral metastases. Through analysis of our database, we aim to elucidate the demographics, radiological characteristics and prevalence of miliary cerebral metastases, aiming to improve early detection and, ultimately, patient care.

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METHODS

Ethics Statement

Our study was planned retrospectively. The study was carried out with the permission Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 22.06.2023, Decision No: 2023-06/57). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted using a retrospective cohort design, reviewing approximately 705 contrast enhanced magnetic resonance imaging (MRI) scans performed in a single institution from January 2016 to May 2023. The cohort included patients diagnosed with metastatic diseases but had not undergone surgical intervention or received radiotherapy treatment.

Inclusion Criteria

Patients included in the study were those with confirmed metastatic disease. In the absence of prior surgical or radiotherapy intervention, miliary cerebral metastases were identified on the MRI scans. Only patients with high-quality MRI scans, devoid of artifacts and with complete medical records, were included in the study.

Exclusion Criteria

Patients were excluded from the study if they had undergone surgical treatment or radiotherapy before the MRI scans (n=43). Patients were also excluded if their MRI scans were of poor quality or incomplete or if their medical records were incomplete or missing (n=12) and with isolated calvarial metastasis (n=32). As a result, 618 brain metastasis cases were included in the study.

In our cohort, miliary cerebral metastases were identified in 6 of the metastatic patients, allowing for a more focused examination of the condition's characteristics and clinical course.

Each patient's demographic information, primary malignancy, and MRI characteristics were meticulously analyzed and recorded. In addition, simultaneous non-contrast computed tomography (CT) images of the patients were also evaluated. This comprehensive approach allowed us to gain significant insights into miliary cerebral metastases' prevalence, manifestations, and imaging characteristics in patients with metastatic disease.

Radiological Technique

All examinations were performed on a 1.5 T MR scanner (Signa Exp, GE Medical Systems) using a 16-channel HNS (head-neck-spine) coil. Before contrast administration, a standard MR examination was carried out including axial T1-weighted images, axial, coronal, and sagittal T2-weighted images as well as axial FLAIR images and DWI. According to the standard protocol, a post-contrast 3D T1W sequence is always required. During the whole MRI examination, the patients were instructed to keep their eyes closed. No sedation or anesthesia was used in any of the patients.

Miliary metastases were identified based on detecting numerous small, disseminated hyperintense lesions on post-contrast T1-weighted images. The lesions were generally less than 2 mm in diameter, uniformly enhancing, and diffusely scattered throughout the brain, often with a predilection for the grey-white matter junction.

Two experienced neuroradiologists blinded to the clinical information independently reviewed radiological data. Regarding discrepancy, a third opinion was obtained from a senior neuroradiologist. This ensured objectivity and minimized bias in the interpretation of imaging findings.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of the patients. The prevalence of miliary cerebral metastases was calculated as a proportion of the total cohort. Confidence intervals were computed using the exact binomial method. Finally, potential correlations between the demographic characteristics of the patients and the prevalence of miliary cerebral metastases were explored using appropriate statistical tests.

RESULTS

Out of the 618 MRI scans of patients with metastatic disease that were retrospectively reviewed, six patients with miliary cerebral metastases were identified, resulting in an prevelance rate of 0.9% in our study population. Of these six patients, 4 were males, and 2 were females. The age range of these patients was between 38 and 68 years, with a mean age of 57.8 years.

Primary cancer was lung carcinoma in 3 patients (50%), breast carcinoma in 2 patients (33.3%), and malignant melanoma in 1 patient (16.6%). While 2 of 3 patients with primary lung cancer were adenocarcinoma, 1 was small cell lung carcinoma. Of the 2 patients with primary breast cancer, both had invasive ductal carcinoma.

No miliary metastasis pattern was observed in the simultaneous non-contrast computed tomography (CT) examination in any patient. In T2-weighted and FLAIR sequences, all of the lesions were iso-hyperintense signal. Lesions could not be detected on pre-contrast T1-

weighted sequences. While the lesions showed diffusion restriction in 2 of 6 patients (33.3%), restricted diffusion was not observed in the lesions in 4 patients (66.6%).

These demographic and radiological characteristics have been summarized in **Table 1**. Exemplary cases are presented in **Figure 1**.

DISCUSSION

Miliary cerebral metastases are a rare and often underdiagnosed form of brain metastasis. The prevelance rate in our study was determined to be 0.9%, a rate that aligns with the rarity highlighted in the literature. This pattern of metastasis has been reported across various primary cancers, such as lung, breast, and gastrointestinal tumors.[4-9,12-22]

Radiologically, the miliary cerebral metastases were characterized as multiple small, disseminated hyperintense lesions on post-contrast T1-weighted images. The lesions were uniformly enhancing, usually less than 2 mm in diameter, and were diffusely scattered throughout the brain. Predominantly, the lesions were located at the grey-white matter junction.

The clinical presentation of miliary cerebral metastases can often mimic infectious diseases like miliary tuberculosis, leading to potential diagnostic confusion.[8,12] The unique radiological characteristics identified in our study, such as small, uniformly enhancing lesions scattered diffusely throughout the brain, were congruent with those reported in earlier studies.[1,2,15-17,20]

Radiological features of miliary cerebral metastases, both in computed tomography (CT) and magnetic resonance imaging,[21] play a pivotal role in their identification. In CT scans, the nodules are practically invisible without enhancement. When intravenous contrast is administered, a small proportion of the nodules exhibit enhancement and can be subtly identified, underscoring the importance of contrast-enhanced CT in these cases.[15]

Table 1. Demographic characteristics, primary cancer information and Radiologic findings of patients with miliary brain metastases

Patient	Age	Gender	Primary	Subtype	Non-enhanced CT	T2-Signal	FLAIR Signal	Pre-contrast T1	DWI
1	60	M	Lung	Adenocarcinoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	-
2	38	F	Breast	Invasive ductal carcinoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	-
3	58	F	Breast	Invasive ductal carcinoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	-
4	66	M	Skin	Malignant melanoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	+
5	68	M	Lung	Small cell carcinoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	+
6	57	M	Lung	Adenocarcinoma	Invisible	Iso-hyperintense	Iso-hyperintense	Invisible	-

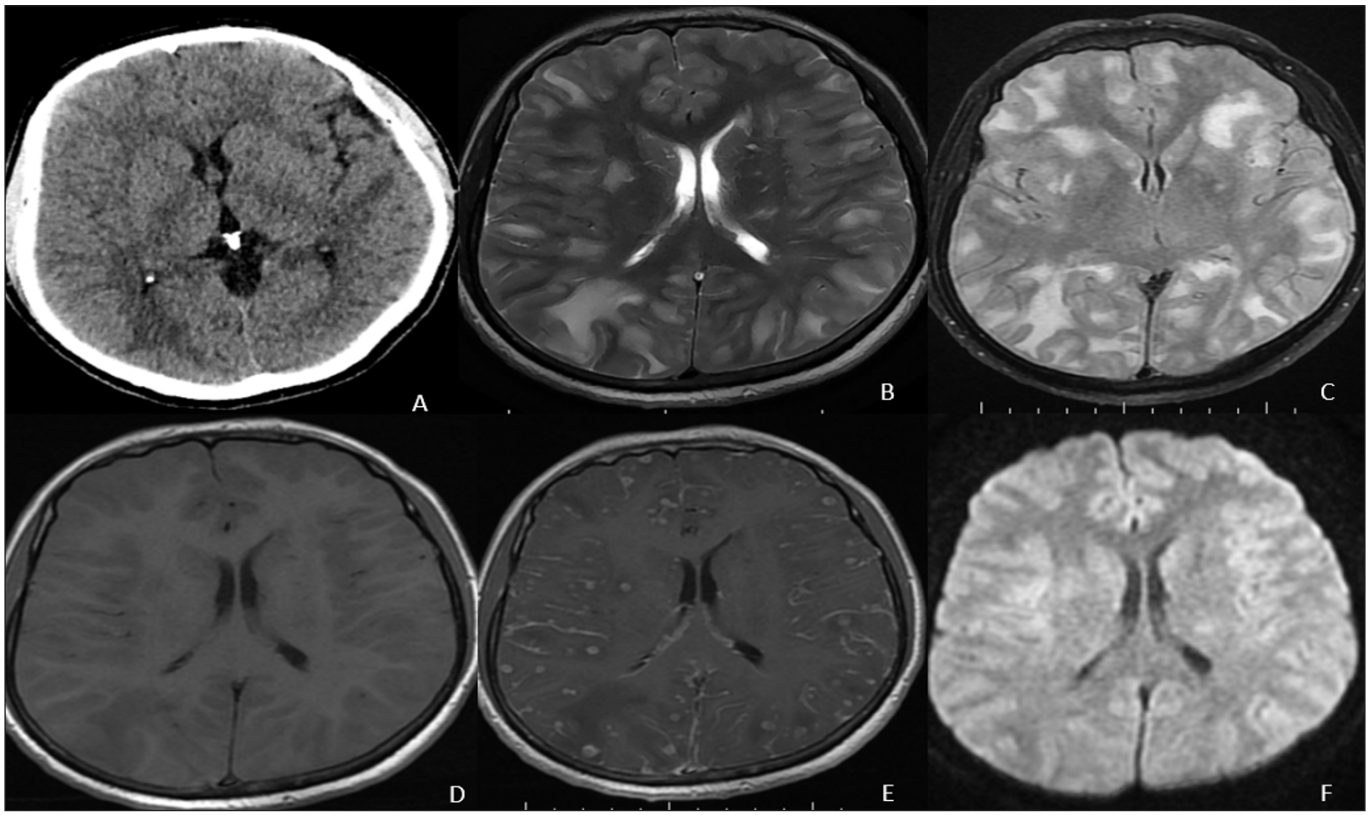

Figure 1: A case of miliary brain metastasis due to lung adenocarcinoma (Patient 1). (A): Axial non-enhanced CT; (B): Axial T2-weighted; (C): FLAIR; (D): Pre-contrast axial T1-weighted; (E): Post-contrast axial T1- weighted; (F): Difusion weighted images.

Regarding MRI, the nodules generally demonstrate mild high signal intensity on T2 and FLAIR sequences and are not observable on T1. The key sequence for demonstrating the extent and distribution of the disease is after contrast administration, where the nodules display avid homogeneous enhancement.[15] Hence, examining MRI images, particularly contrast-enhanced sequences, is critical for detecting miliary cerebral metastases.

Although the characteristic enhancement pattern of miliary brain metastases has been presented with case reports in the literature, few cases of miliary brain metastasis that was hyperintense on T2 and FLAIR sequences and did not show significant contrast enhancement after Gadolinum injection was also presented in the literature.[6,23]

The response and prognosis of miliary cerebral metastases to various treatments, including targeted therapies and radiotherapy, remains poorly understood.[5,11,18,19] In this context, it is crucial to note that most of our patients were untreated before scanning, which further substantiates the necessity for early detection of this rare form of metastasis.

While this study has provided valuable insights into the prevelance, demographics, and radiological features of miliary cerebral metastases, several limitations exist. Firstly, the study's retrospective nature and the small sample size potentially limit the generalizability of our findings to a broader population. Additionally, the study's reliance on medical records could have resulted in incomplete data or reporting bias. Secondly, we could not perform a survival analysis due to the study design, limiting our understanding of the prognostic implications of miliary cerebral metastases. Lastly, the lack of post-mortem histopathological confirmation is a significant limitation in most cases, as it could lead to potential diagnostic inaccuracy.

Given these limitations, future research should prospectively recruit larger cohorts, incorporate survival analysis, and, if possible, perform post-mortem histopathological confirmation to provide more definitive evidence of miliary cerebral metastases.

CONCLUSION

Miliary cerebral metastases, although rare, pose a significant challenge regarding accurate diagnosis and effective management. This study provides an in-depth look into the demographic and radiological characteristics of this unique form of metastasis. Our findings underline the critical role of clinical suspicion and advanced imaging in ensuring timely diagnosis. They also emphasize the urgent need for further research to develop effective therapeutic strategies and to improve our understanding of the prognosis associated with this condition. Enhancing our comprehension of miliary cerebral metastases will enable more personalized patient care and potentially improved patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 22.06.2023, Decision No: 2023-06/57).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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