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A Case of Thymic Carcinoma with Bone and Cerebral Metastases Treated with Stereotactic Radiosurgery and Chemotherapy

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Conflict of interest: None declared

Patient: Female, 63
Final Diagnosis: Thymic carcinoma
Symptoms: Hip pain
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: Thymic carcinoma is a rare malignant neoplasm. High-grade thymic carcinoma has a high recurrence rate following surgery, and a low 5-year survival rate. Approximately 30% of patients with thymic carcinoma will be asymptomatic at the time of diagnosis. Extrathoracic metastasis on presentation is uncommon. Treatment of the primary tumor includes surgery, chemotherapy, and fractionated radiation. A rare case of thymic carcinoma that presented with bone and cerebral metastases is reported in a patient who responded well to stereotactic radiosurgery and chemotherapy.

Case Report: A 63-year-old woman presented to the hospital for evaluation of hip pain. She was diagnosed with a lytic bone lesion of the right femur and brain metastasis. Biopsies from the mediastinal mass and right femur showed histological features consistent with carcinoma. Immunohistochemistry showed positive immunostaining of the tumor cells for the c-kit receptor (CD117) and CD5, supporting a diagnosis of stage IVb thymic carcinoma. Treatment included stereotactic radiosurgery, which delivered multiple radiation beams to the tumor tissue from different directions to target the tumor without affecting normal tissues. She was treated as an outpatient with carboplatin and taxol after stereotactic radiosurgery. The patient recovered well following treatment.

Conclusions: A case of thymic carcinoma with bone and cerebral metastases was successfully treated with stereotactic radiosurgery and chemotherapy.

MeSH Keywords: Brain Neoplasms • Radiosurgery • Thymus Neoplasms

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Background

Thymic carcinoma is an extremely rare malignancy that belongs to the group of thymic epithelial neoplasms that include thymoma, thymic carcinoma, and thymic neuroendocrine carcinoma. In 2008, the annual incidence of thymic epithelial neoplasms was reported by the Netherlands Cancer Registry to be 0.15–0.32 per 100,000 person-years, and thymic carcinoma accounted for only 1–4% of these cases [1]. Only 7% of cases of thymic carcinoma present with extrathoracic spread, with cerebral metastasis being very rare [2].

Stage 3 and stage 4 thymic carcinoma is usually treated with surgery and platinum-based chemotherapy [3]. Patients with incompletely resected thymic carcinoma and recurrent high-grade tumors may also receive fractionated radiotherapy [3]. Currently, there are no clinical guidelines for the management of cerebral metastases from thymic carcinoma, and there are no studies on survival data that allow prediction of patient prognosis. Surgery, chemotherapy, and fractionated radiotherapy have all been used to treat patients with metastatic thymic carcinoma, but with mixed results [3]. However, recent reports suggest that stereotactic radiosurgery may become an important option in the management of patients with thymic carcinoma and brain metastasis who meet the criteria for stereotactic radiosurgery [4]. Stereotactic radiosurgery results in selective irradiation of a sharply defined target within the brain, with less damage to surrounding tissue.

Thymic carcinoma is an uncommon malignancy that has varied histologic subtypes with different biological behavior [5,6]. Currently, the World Health Organisation (WHO) histological classification of thymic carcinoma includes the subtypes of squamous cell carcinoma, lymphoepithelioma-like carcinoma, mucoepidermoid carcinoma, basaloid carcinoma, sarcomatoid carcinoma, clear cell carcinoma, and mixed small cell undifferentiated thymic carcinoma [6].

This report if of a case of thymic carcinoma in a 63-year-old woman who presented with cerebral and bone metastases and who responded well to stereotactic radiosurgery and chemotherapy.

Case Report

A 63-year-old Caucasian woman presented to the emergency department with progressively worsening right hip pain during the past five months. She had a positive family history of malignancy. Her father had been diagnosed with colon cancer at 58 years of age, and her mother had uterine cancer at 69 years of age. The patient has a 40 pack-year smoking history and occupational exposure to lime rock while working in construction. Her past medical history was positive only for hypertension and hyperlipidemia.

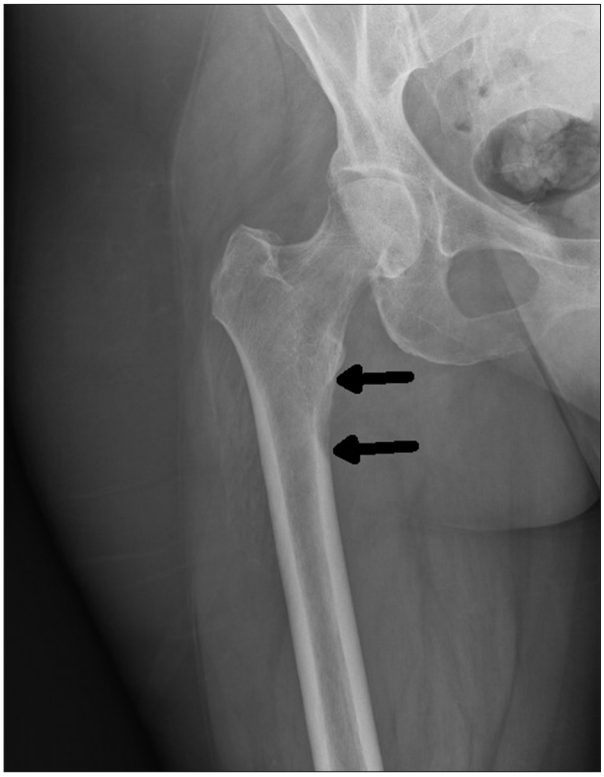

Figure 1. X-radiograph of the right femur. A lytic lesion is present in the medial subtrochanteric proximal femoral diaphysis (arrows).

On admission to hospital, her vital signs were stable and basic laboratory investigations were unremarkable. Physical examination identified a palpable, non-tender, non-fluctuant, soft, 7 cm mass on the anterior chest wall that had been present for more than a year. The patient also had tenderness to palpation along the right thigh with a limited range of motion and an antalgic gait, indicating pain on weight-bearing.

An X-ray of the right femur showed a lytic lesion in the medial subtrochanteric proximal right femoral diaphysis that was suspicious for a bone metastasis (Figure 1). Computed tomography (CT) of the chest, abdomen, and pelvis showed approximately ten scattered bilateral pulmonary nodules, with the largest measuring 2 cm in diameter (Figure 2), and a sternomanubrial lytic lesion with a 5 cm soft tissue mass extending to the superior mediastinum. The patient underwent interventional imaging-guided core biopsy of the mediastinal mass. The preliminary histopathological diagnosis of the mediastinal mass was of infiltrating non-small cell carcinoma (Figure 3).

Further studies were performed, including immunohistochemistry for CD5 (Figure 4), the c-kit receptor (CD117), PAX8, GATA-3,

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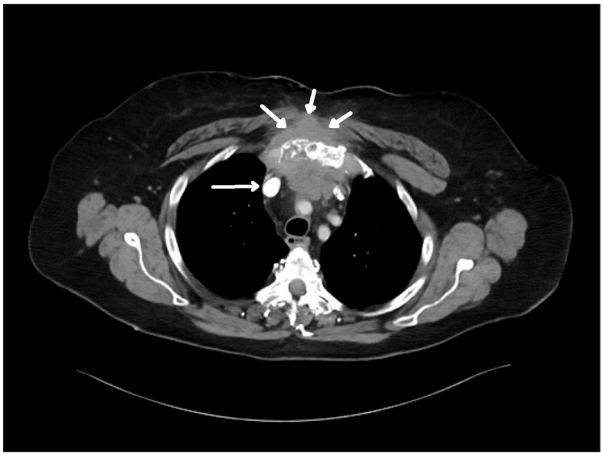

Figure 2. Computed tomography (CT) image of the chest. Chest CT performed with 50 cc of intravenous Omnipaque-300. Bilateral scattered pulmonary nodules are present with the largest in the left lower lobe measuring 2 cm (white open arrowhead). A sternomanubrial lytic lesion is present with an associated 5 cm soft tissue mass extending to the superior mediastinum (three closed arrowheads).

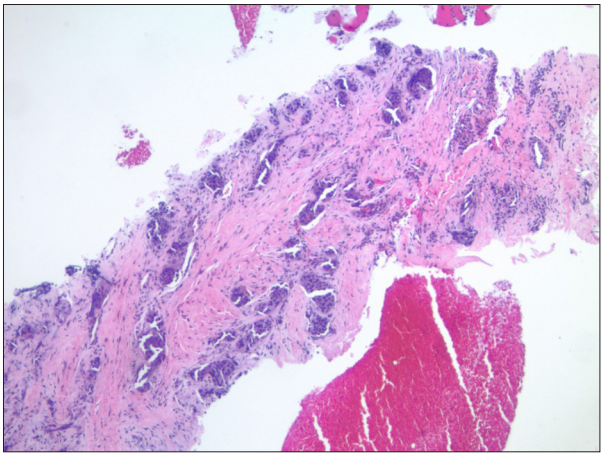

Figure 3. Photomicrograph of the histology of the mediastinal biopsy. Photomicrograph of the histology of the mediastinal biopsy shows multiple foci of invasive carcinoma in a desmoplastic stroma. The tumor cells show cytology atypia and features of a high-grade carcinoma. Hematoxylin and eosin (H&E). Magnification ×40.

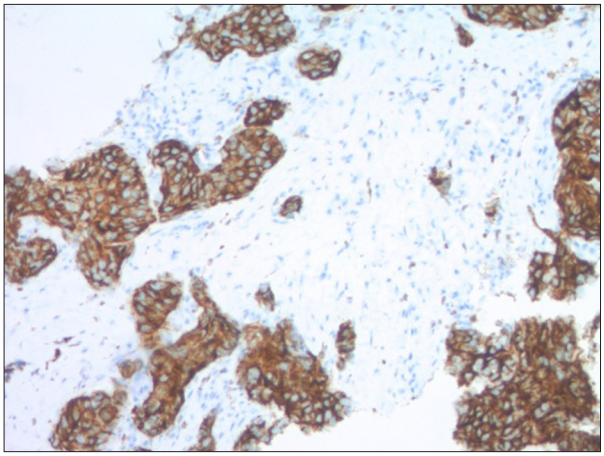

Figure 4. Photomicrograph of the immunohistochemistry of the mediastinal biopsy. Photomicrograph of the immunohistochemistry of the mediastinal biopsy shows tumor cells with strong CD5 immunostaining (brown). CD5 and CD117 immunopositivity support a diagnosis of primary thymic carcinoma. Magnification ×40.

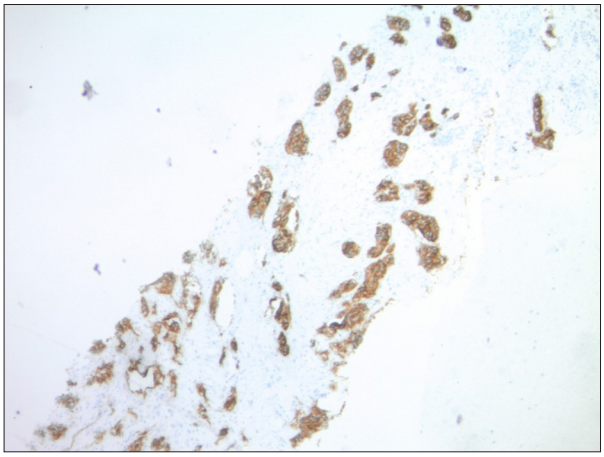

Figure 5. Photomicrograph of the immunohistochemistry of the mediastinal biopsy. Photomicrograph of the immunohistochemistry of the mediastinal biopsy shows tumor cells with strong positive immunostaining for the c-kit receptor (CD117) (brown). CD5 and CD117 immunopositivity support a diagnosis of primary thymic carcinoma. Magnification ×40.

cytokeratin 7, thyroid transcription factor, CD20, and p63. Immunohistochemistry showed that the carcinoma cells were positive for CD5 and CD117 (Figure 5), and negative for other immunomarkers in the panel, which supported a diagnosis of a metastasis from a primary thymic carcinoma rather than a non-small cell lung cancer (NSCLC). Histologically, the tumor cells were high-grade (poorly-differentiated). The tumor subtype was not assigned because the cells were crushed during the biopsy procedure.

An orthopedic surgical opinion was sought to assess the need for surgical intervention due to the high femoral fracture risk. The patient underwent an elective open femoral reduction and internal fixation for impending pathological fracture, and bone biopsy was taken from the tumor in the right femur. The histology and immunohistochemistry findings were also consistent with a diagnosis of metastatic thymic carcinoma.

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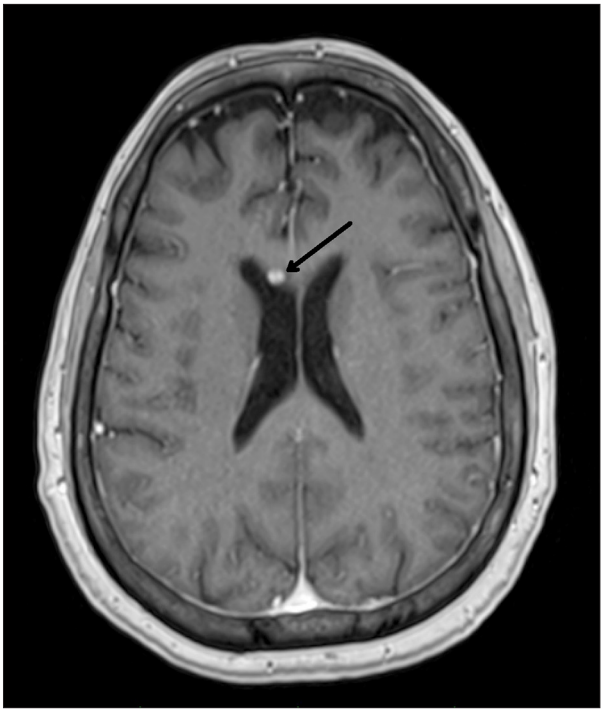

Figure 6. Magnetic resonance imaging (MRI) of the brain before treatment. Multiplanar multisequence MRI images of the brain with intravenous gadolinium. An enhancing 6 mm nodule of the right corpus callosum (arrow) is shown, indicating intracranial metastasis. There is no sign of intracranial hemorrhage.

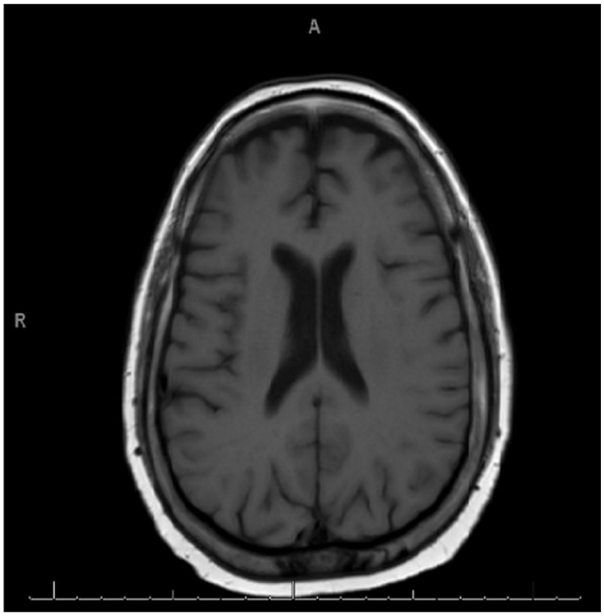

Figure 7. Magnetic resonance imaging (MRI) of the brain after treatment. MRI imaging of the brain post-treatment shows interval resolution of previously noted enhancing lesions involving right anterior corpus callosum as well as right middle/inferior frontal gyral margins.

Further staging and clinical workup included magnetic resonance imaging (MRI) of the brain, which identified a solitary 6 mm nodule in the right corpus callosum, which was suspicious for intracranial metastasis (Figure 6). A neurosurgical opinion was obtained, but and neurosurgical intervention was deferred until her workup and treatment plan were completed. Medical oncology and radiation oncology were consulted while she was an inpatient. Outpatient positron emission tomography (PET) imaging followed by stereotactic radiation therapy to the brain, bone, and possibly anterior mediastinum and palliative chemotherapy with platinum-based chemotherapy and taxol were recommended.

The patient was discharged to home on postoperative day 6 with a diagnosis of Stage IVb thymic carcinoma, with outpatient follow-up by her oncology team. She commenced palliative chemotherapy with carboplatin and taxol and opted to receive stereotactic radiosurgery after discussion of the radiation therapy options. The mapped brain metastasis was treated with two fractions of hypofractionated Gamma Knife radiosurgery with a median dose of 20 Gy at 50% isodose line (total dose, 40 Gy) and a total beam-on time after patient setup of 13.8 min. Eight months following Gamma Knife treatment, her brain MRI was negative (Figure 7). Fourteen months from the initial diagnosis, the mass in her chest had decreased in size by 2 cm. She underwent radiation treatment for pain to the right hip. At the time of writing this report, the patient has had no neurocognitive functional decline, is doing well, and continues to attend outpatient follow-up.

Discussion

This case report has shown that thymic carcinoma is an uncommon malignancy with varied histological subtypes [6], and unpredictable biological behavior [5]. The presence of extrathoracic metastases are uncommon at presentation, and cerebral metastasis is rare [6]. Fewer than 50 cases of cerebral metastasis associated with a primary thymic carcinoma have been reported in the literature [4]. Because thymic carcinoma is rare, there is no consensus on a treatment protocol for advanced-stage thymic carcinoma, and treatment is based on clinicians' experience, preference, and a few published clinical reports.

However, there are some documented prognostic factors associated with patient outcome in thymic carcinoma. The presence of high tumor grade (poor differentiation) on histology is associated with significantly reduced patient survival is an indicator of an aggressive clinical course and a high incidence of local recurrence [7]. High-grade primary thymic malignancies have been reported to be associated with median

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survival times of only 11 months compared with 25.4–49.0 months in patients with low-grade primary thymic malignancies [7]. Another prognostic indicator is the successful and complete surgical resection of the primary thymic tumor. In 2002, Ogawa et al. [7] reported that 75% of patients who were treated with complete resection were alive and tumor-free at the last follow-up. However, the most important prognostic indicator is tumor stage. Using the Masaoka classification system [8], the 5-year survival rate of for stage IVb thymic carcinoma with extrathoracic spread is 30% [3].

The patient in this report presented with the most serious combination of risk factors for poor clinical outcome. She had a high-grade thymic carcinoma that was not amenable to complete surgical resection, and she had a stage IVb tumor. This report highlights the approach to the treatment of this patient, who had late-stage thymic carcinoma and brain metastasis. The most commonly reported treatment for stage III and stage IV thymic carcinoma are multimodal and include platinum-based chemotherapy, neoadjuvant chemotherapy, surgery, and postoperative radiotherapy [9]. Complete resection of the tumor is important, when possible, and neoadjuvant chemotherapy is of benefit [9]. Unfortunately, in this reported case, complete surgical resection was not possible.

Because late-stage thymic carcinoma is rare, there are no established guidelines on the most effective approach to chemotherapy. However, there have reports on the use of platinum-based chemotherapy, including cisplatin, possibly combined with doxorubicin [9–11]. Fractionated radiation has also been used, and several reports have indicated that thymic carcinoma is highly radiosensitive [10,11]. In 2002, Ogawa et al. reported that postoperative radiotherapy was effective in preventing local recurrence in patients treated with complete surgical resection [7]. However, the current clinical consensus is that radiotherapy is used only in cases of incomplete resection, high-grade histology, and where the tumor is aggressive and invades the surrounding structures. Treatment with whole-brain irradiation for metastasis from thymic carcinoma carries a significant risk of side effects. Therefore, alternative treatment methods should be considered.

Stereotactic radiosurgery allows multiple radiation beams to be delivered to the tumor tissue from different directions and can define the tumor target, which spares the surrounding normal tissue from the effects of ionizing radiation. Whether stereotactic radiosurgery is effective in brain metastasis from thymic carcinoma is unknown. Tumor size, proximity to the cranial nerves, and location of the tumor are important variables in determining whether to recommend stereotactic radiosurgery for brain metastasis [12–14]. This patient had a 6 mm cerebral nodule that was distant from sensitive cranial nerves and was located in the white matter of the brain. These variables predicted safe stereotactic radiosurgery with reasonable success. A further important advantage of stereotactic radiosurgery is the preservation of neurocognitive function when compared with fractionated radiation of the entire cerebrum. Irradiation of normal cerebrum significantly affects neurocognitive function in a dose-dependent manner, while stereotactic radiosurgery reduces the decline in neurocognitive function, assuming that other treatment elements are favorable [15].

Recently, new strategies for the treatment of thymic carcinoma have been investigated, including targeted therapy for tumors that express epithelial growth factor receptor (EGFR) mutations, c-KIT mutations, and insulin-like growth factor receptor 1 (ILGFR1) mutations, despite the expression of these mutations being rare [5,16]. Currently, there are no prospective clinical trials on treatment options for thymic carcinoma [16].

Conclusions

Thymic carcinoma is a complex malignancy that includes varied histological subtypes and histological grades that are associated with a spectrum of tumor behavior, from indolent to highly aggressive. Even with high-grade histology, thymic carcinoma rarely metastasizes to the brain. Treatment options are limited due to the lack of controlled large-scale clinical trials and clinical studies, as this malignancy is rare, but a multimodality treatment approach is used most often. Recently, stereotactic radiosurgery has been used to treat brain metastasis in primary thymic carcinoma, and as this case report has shown, this treatment may result in good clinical outcome.

Conflict of interest

None.

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