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Case Report

Invasive thymoma metastatic to the cavernous sinus

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Abstract

Background: Thymomas are typically benign tumors of thymic epithelium. Metastases to distal sites, particularly intracranial locations, are extremely rare. Herein, we present the third case of thymoma and the second invasive thymoma to metastasize to the cavernous sinus, adjacent to the pituitary.

Case Description: A 41-year-old female patient presented with headaches, stuffy nose, and drooping of the right face. A magnetic resonance imaging scan revealed a complex, multilobulated mass centered upon the right cavernous sinus. The mass was removed via transsphenoidal surgery, and histopathological investigation confirmed the diagnosis of metastatic thymoma. A positron emission tomography-computed tomography scan demonstrated a large anterior mediastinal mass. A biopsy confirmed the diagnosis of invasive thymoma morphologically identical to the World Health Organization type B2 sellar region metastasis.

Conclusion: Although rare, thymomas can metastasize to the central nervous system. Our case is the second invasive thymoma to metastasize to the cavernous sinus, adjacent to the pituitary.

Key Words: Cancer, immunohistochemistry, metastatic tumor, pathology, sellar metastases, thymoma

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INTRODUCTION

Thymomas are typically benign tumors of thymic epithelium. They are classified as malignant when invasive beyond the thymic capsule. Defined as such, up to 36% of thymomas are malignant. Most show only local invasion. Metastases to distant sites are infrequent, occurring in less than 3% of malignant thymomas.[5] Metastasis to the central nervous system (CNS), particularly to the cavernous sinus adjacent to the pituitary, occurs only rarely. There have been only two reports of thymoma metastatic to the pituitary.[9,25] Herein, we present the third case and review the literature.

CASE REPORT

In February 2010, a 41-year-old female presented with a 6-week history of headaches, nasal congestion, epistaxis,

difficulty opening her mouth and ptosis of the right eyelid. A magnetic resonance imaging (MRI) scan revealed a complex multilobulated mass centered within the right cavernous sinus, the cavernous internal carotid artery being encased [Figures 1 and 2]. Laterally, the tumor extended to the petrous bone and partially encased the right petrous carotid artery. Also noted was tumor extension into Meckel's cave, the right prepontine cistern and masticator space via the course of the second branch of the trigeminal nerve. The differential diagnosis included meningioma, and metastatic disease. The rapid progression of symptoms and the atypical imaging appearance of the lesion strongly suggested the latter. In that the tumor lay just lateral to the pituitary gland, a diagnosis of pituitary adenoma was unlikely.

Transsphenoidal surgery was undertaken to obtain a tissue diagnosis and to debulk the mass. Postoperative adjuvant chemotherapy was administered (Cytoxan, Adriamycin). The patient is considering adjuvant radiation therapy.

MATERIALS AND METHODS

The formalin-fixed, routinely processed specimen was cut at 5 μm and stained with hematoxylin and eosin (H and E), the Gomori reticulin method, and the periodic acid-Schiff method with and without diastase digestion. Immunohistochemistry (streptavidin–biotin peroxidase complex method) utilized antisera directed against epithelial membrane antigen (EMA; Dako, Carpinteria, CA; 1:20, E29) keratin (AE1–AE3; Zymed, South San Francisco, CA; 1:200), vimentin (Dako; 1:500, 3B4), chromogranin (Roche, Indianapolis, IN; 1:1000, LK2H10), S-100 protein (Dako; 1:800, polyclonal), p53 protein (Dako; 1:200, DO-7), and Ki-67 (MIB-1; Dako; 1:800).

Histologically, sections revealed a lympho-epithelial tumor [Figure 3a], the epithelial component of which was immunopositive for the high molecular weight keratin [Figure 4], P63, and CD57, but negative for germ cell markers (Oct3/4, PLAP, AFP), synaptophysin, S100 protein, and estrogen as well as progesterone receptor. The lymphoid component consisted mainly of small,

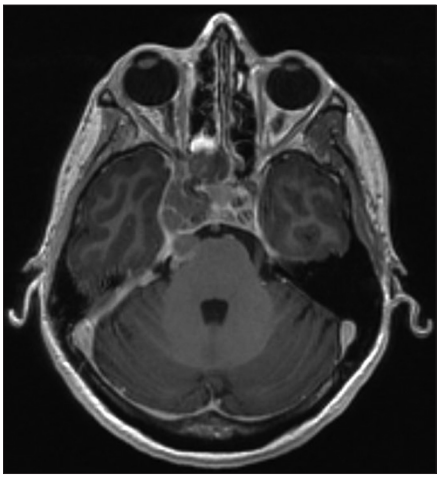

Figure 1: Axial T1 weighted magnetic resonance imaging scan showing a complex multilobulated mass centered within the right cavernous sinus and encasing the cavernous internal carotid artery

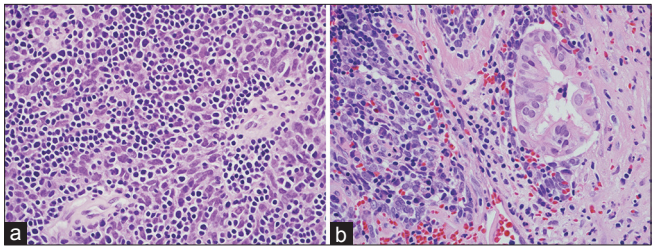

Figure 3: H and E staining of sellar mass and anterior mediastinal mass. (a) Light microscopic features of the pituitary mass. Original magnification: ×100. (b) Light microscopic features of the anterior mediastinal mass identical to those of pituitary mass. Original magnification: ×100

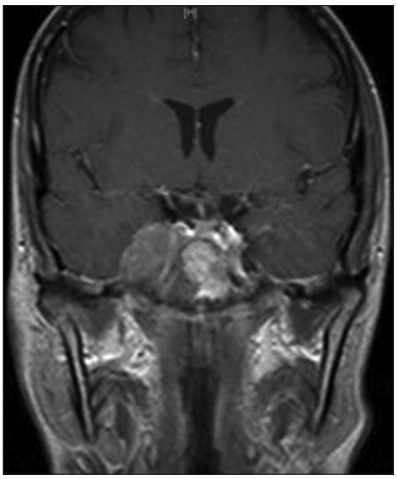

Figure 2: Coronal T1 weighted magnetic resonance imaging scan showing a complex multilobulated mass centered within the right cavernous sinus and encasing the cavernous internal carotid artery

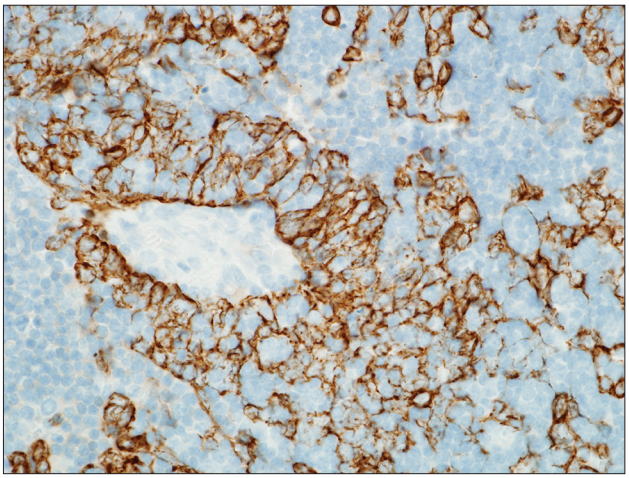

Figure 4: Sellar epithelial cells show immunopositivity for high molecular weight keratin. Immunostaining for P63. Original magnification: ×200

cytologically benign lymphocytes immunopositive for terminal deoxytransferase (TdT) (Supertechs, Bethesda, MD; 1:100, polyclonal), CD1a (Coulter, Westbrook, ME; 1:10, Clone O10), CD3 (Novocastra, Burlingame, CA; 1:50, Clone PS1), CD4 (Novocastra, 1:600, Clone 4B12), CD5 (Novocastra, 1:100, Clone 4C7), CD8 (Dako, 1:100, Clone C8/144B) and CD99 Dako, 1:100, Clone 12E7), indicating an immature T-lymphocyte (thymocyte) phenotype. *In situ* hybridization for Epstein–Barr virus-encoded RNA was also negative.

Flow cytometric evaluation with gating of lymphocytes showed cell viability to be low (18%). Almost all intact cells recovered (97%) were lymphocytes. As with the immunohistochemical stains [Figure 5a-d], the majority were immature T-cells coexpressing CD4, CD8, and TdT. The B cell population was scant with no suggestion of an abnormal or clonal B cell processes.

A positron emission tomography-computed tomography (PET-CT) scan of the mediastinum demonstrated a large (9.8 × 6.9 × 4.4 cm) anterior mediastinal mass [Figure 6]. Histological examination of the specimen revealed an invasive thymoma (World Health Organization [WHO] type B2) with features identical to those of the cavernous sinus metastasis [Figure 3b]. On the basis of radiographic and histologic findings, a diagnosis of invasive thymoma was made.

DISCUSSION

Thymoma and lymphoma are the most frequently occurring thymic tumors. The former are defined as tumors of thymic epithelium. Their classification is a controversial topic[20] in that several classification schemes exist and are in current use. Categories of thymic epithelial tumor include encapsulated and invasive thymomas, as well as thymic carcinoma. It is not possible to distinguish between an encapsulated and invasive thymoma on histologic examination of the tumor cells alone. Invasive thymomas simply feature invasion beyond the thymic capsule. In contrast, invasive thymomas and thymic carcinomas are distinguishable on histologic features of the tumor cells. Masaoka *et al*. developed a staging categorization of thymic tumors, one subsequently modified[11,15] and shown to correlate well with prognosis.[3] Briefly, tumors of stage I are encapsulated and contained within the thymus, stage II lesions penetrate the capsule to involve fatty tissue, stage III tumors extend into neighboring tissues or organs, stage IVa examples spread widely to involve pleura and/or pericardium (thoracic spread), and stage IVb lesions have metastasized to distant organs (extra-thoracic spread). The WHO has formulated a different classification of thymic tumors, one presently gaining wide acceptance.[21] According to that scheme, thymic epithelial tumors are categorized as type A, types B1 to B3, or carcinoma (type C) depending upon cellular morphology and composition, resemblance to normal thymic cortex, as well as epithelial cell to lymphocyte ratio. Types A and B exhibit low malignant potential, whereas type C is usually frankly malignant. Several other classifications exist,[20] but a detailed discussion is beyond the scope of this publication.

Symptomatic metastases to the pituitary region are uncommon. Most frequent primary sites in women include mammary carcinoma followed by the lung and gastric carcinoma. In men, the most frequent primary tumors include carcinoma of the lung followed by prostate cancer.[24] Metastases of invasive thymoma and thymic carcinomas affect primarily lungs, lymph nodes, and liver.[1,17] Metastasis of thymomas to the brain are rare.[4,13,23,26] To our knowledge, three examples of pituitary metastases of thymoma have been reported. One was a thymoma found to be metastatic to pituitary

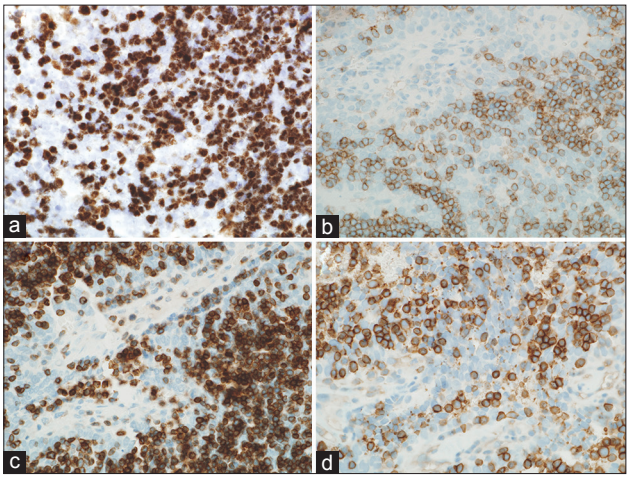

Figure 5: Sellar lymphocytes show immunopositivity for (a) TdT, (b) CD1a, (c) CD3, (d) CD99. Immunostaining for TDT, CD3, CD5, CD99 indicating an immature thymocyte phenotype. Original magnification: ×200

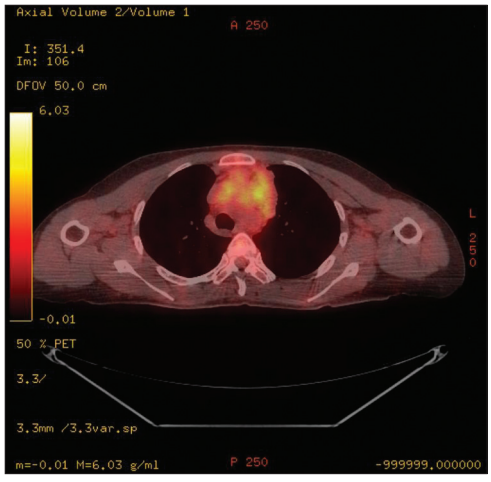

Figure 6: A positron emission tomography computed tomography scan of the mediastinum revealing a large 9.8 × 6.9 × 4.4 cm anterior mediastinal mass

at postmortem examination,[2] and two were thymomas metastatic to the gland and diagnosed during life.[9,25] Of the latter, the case of Kanayama *et al*. involved an 86-year-old male who presented with visual impairment and right-sided ptosis. The primary thymoma was a WHO type B and Masaoka stage 2-3, whereas the metastasis was Masaoka stage 4B. Although the tumor was partially resected by the transsphenoidal approach, the patient died within 6 months with multiple metastases. The second case, that of Wagner *et al*., involved a 61-year-old male with a long-standing thymoma who developed diplopia and left-sided ptosis referable to a sellar lesion. Transsphenoidal resection of the tumor revealed a poorly differentiated squamous cell carcinoma (thymoma, type C) involving the adenohypophysis and pituitary stalk. A CT-guided biopsy of the anterior mediastinal primary revealed squamous cell carcinoma morphologically identical to the pituitary metastasis. The lesion was considered a thymic carcinoma having arisen within a long standing thymoma. Our report is the third case of a thymoma metastatic to the cavernous sinus adjacent to the pituitary during life. Given the low metastatic potential thymomas of type B, our metastasis can be considered a rarity.

Metastases to the sellar region occur via several routes. These include direct hematogenous spread to the pituitary, spread from juxtasellar masses, spread through the suprasellar cisterns, and via the portal vessels.[12] The majority of metastases direct to the pituitary affect the posterior lobe given its direct blood supply via the hypophysial arteries.[24] Metastases to the anterior lobe, although less common, can occur by spread via capsular arteries and interlobular capillaries or by direct extension from dural/osseous deposits.[14,19]

Only 7% of metastases to the pituitary are symptomatic,[24] thus complicating a diagnosis during life. Principle symptoms include diabetes insipidus, headache and visual impairment.[16] In that diabetes insipidus rarely occurs in patients with pituitary adenoma, its presence is a good indication of metastatic disease. Moreover, a history of malignancy, increasing pain and rapid progression of symptoms further support the diagnosis.[8,10] Although MRI is the gold standard for neuroradiologic investigation of brain lesions, metastases do not exhibit a single, distinctive appearance. Instead, they vary from single to multiple, solid to cystic, and hemorrhagic to centrally necrotic. Thus, a firm diagnosis of a sellar metastasis cannot be made on clinical and radiographic grounds alone. Histopathologic investigations, as in our case and others,[19,22] were required for the confirmation.

Patients with invasive thymoma and single metastases to the CNS have a mean survival of only 8.5 months. This further decreases with increasing numbers of metastases.[4] Treatment of patients with sellar metastases includes surgical resection and radiation, as well as chemotherapy. Typically, as in our case, the lesion is resected for the combined purpose of decompression and arriving at a diagnosis. This is often followed by radiation therapy. Gamma-knife radiosurgery has become a widely accepted treatment of metastatic CNS lesions.[18] Thymic carcinomas are chemotherapy-sensitive lesions, 30-50% 5-year survivals being achieved.[7] In cases of thymic neoplasia, the mediastinal mass can be effectively treated by chemotherapy, surgery, and radiation therapy.[6] Thymomas are known to be associated with immunologic disorders, such as myasthenia gravis, and secondary neoplasms including colorectal, pulmonary and thyroid tumors.[27] Despite the relatively short survival of these patients, aggressive and multimodal therapy to both the sellar and mediastinal lesions is recommended.[4]

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REFERENCES

1. Al-Barbarawi M, Smith SF, Sekhon LH. Haemorrhagic brain metastasis from a thymic carcinoma. J Clin Neurosci 2004;11:190-4.
2. Butterworth ST, Newell JE, Stack BH. Malignant thymoma with central nervous system metastases. Br J Dis Chest 1973;67:141-5.
3. Dawson A, Ibrahim NB, Gibbs AR. Observer variation in the histopathological classification of thymoma: Correlation with prognosis. J Clin Pathol 1994;47:519-23.
4. Ersahin M, Kilic K, Gogusgeren MA, Bakirci A, Vardar Aker F, Berkman Z. Multiple brain metastases from malignant thymoma. J Clin Neurosci 2007;14:1116-20.
5. Gatzimos KR, Moriarty AT, Pingleton JM, McCloskey DW. Diagnosis of metastatic thymoma using flow cytometry. Pathobiology 1992;60:168-72.
6. Geffen DB, Benharroch D, Yellin A, Ariad S, Or R, Cohen Y. Multimodal treatment of metastatic thymic carcinoma including high-dose chemotherapy with autologous stem cell transplantation: Report of a case with more than 4-year disease-free survival. Am J Clin Oncol 2001;24:566-9.
7. Hanna N, Gharpure VS, Abonour R, Cornetta K, Loehrer PJ, Sr. High-dose carboplatin with etoposide in patients with recurrent thymoma: The Indiana University experience. Bone Marrow Transplant 2001;28:435-8.
8. Juneau P, Schoene WC, Black P. Malignant tumors in the pituitary gland. Arch Neurol 1992;49:555-8.
9. Kanayama S, Matsuno A, Nagashima T, Ishida Y. Symptomatic pituitary metastasis of malignant thymoma. J Clin Neurosci 2005;12:953-6.
10. Kattah JC, Silgals RM, Manz H, Toro JG, Dritschilo A, Smith FP. Presentation and management of parasellar and suprasellar metastatic mass lesions. J Neurol Neurosurg Psychiatry 1985;48:44-9.
11. Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, Goya T, *et al*. A review of 79 thymomas: Modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 1994;44:359-67.
12. Komninos J, Vlassopoulou V, Protopapa D, Korfias S, Kontogeorgos G, Sakas DE, *et al*. Tumors metastatic to the pituitary gland: Case report and literature review. J Clin Endocrinol Metab 2004;89:574-80.

13. Kong DS, Lee JI, Nam DH, Park K, Suh YL. Cerebral involvement of metastatic thymic carcinoma. J Neurooncol 2005;75:143-7.
14. Kovacs K. Metastatic cancer of the pituitary gland. Oncology 1973;27:533-42.
15. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
16. Morita A, Meyer FB, Laws ER, Jr. Symptomatic pituitary metastases. J Neurosurg 1998;89:69-73.
17. Nickels J, Franssila K. Thymoma metastasizing to extrathoracic sites. A case report. Acta Pathol Microbiol Scand A 1976;84:331-4.
18. Nicolato A, Ferraresi P, Bontempini L, Tomazzoli L, Magarotto R, Gerosa M. Multiple brain metastases from "lymphoepithelioma-like" thymic carcinoma: A combined stereotactic-radiosurgical approach. Surg Neurol 2001;55:232-4.
19. Ramsay JA, Kovacs K, Scheithauer BW, Ezrin C, Weiss MH. Metastatic carcinoma to pituitary adenomas: A report of two cases. Exp Clin Endocrinol 1988;92:69-76.
20. Rieker RJ, Hoegel J, Morresi-Hauf A, Hofmann WJ, Blaeker H, Penzel R, *et al*. Histologic classification of thymic epithelial tumors: Comparison of established classification schemes. Int J Cancer 2002;98:900-6.
21. Rosai J, Sobin L. WHO Histological Typing of Tumors of the Thymus. Berlin: Springer; 1999.
22. Ruelle A, Palladino M, Andrioli GC. Pituitary metastases as presenting lesions of malignancy. J Neurosurg Sci 1992;36:51-4.
23. Tamura Y, Kuroiwa T, Doi A, Min KY. Thymic carcinoma presenting as cranial metastasis with intradural and extracranial extension: Case report. Neurosurgery 2004;54:209-11.
24. Teears RJ, Silverman EM. Clinicopathologic review of 88 cases of carcinoma metastatic to the putuitary gland. Cancer 1975;36:216-20.
25. Wagner KB, Khan A, Mir R, Herman PG. Thymic carcinoma arising from long standing thymoma and presenting with pituitary metastases. Comput Med Imaging Graph 1991;15:411-4.
26. Wick MR, Scheithauer BW, Weiland LH, Bernatz PE. Primary thymic carcinomas. Am J Surg Pathol 1982;6:613-30.
27. Wilkins KB, Sheikh E, Green R, Patel M, George S, Takano M, *et al*. Clinical and pathologic predictors of survival in patients with thymoma. Ann Surg 1999;230:562-72.