Metastatic Disease to the Clivus Mimicking Clival Chordomas

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Abstract

Objectives/Hypothesis A comprehensive review of the literature of clival metastases and presentation of two additional cases.

Study Design Literature review and report of two cases.

Methods A literature review of the MEDLINE database (1950 to January 19, 2013) was performed to identify all cases of patients with metastatic disease to the clivus. Additionally, two novel cases are presented.

Results In total, 47 cases were identified in the literature, including the two cases presented in this study. Metastatic disease to the clivus is the initial presenting symptom of the primary malignancy in 36% (13/36) of the cases. When there was a history of malignancy, the median interval of time to clival metastases was 24 months (range 1 to 172 months). Clinical symptoms manifested often as cranial neuropathies, with at least abducens palsies as the initial presenting symptom in 61.9% (26/42) of patients. Tumor pathology was diverse, but several pathologies were seen more commonly: prostate carcinoma (18.1%, 9/47), hepatocellular carcinoma (10.6%, 5/47), and thyroid follicular carcinoma (8.5%, 4/47).

Conclusion Although clival metastases are extremely rare, they are an important part of the differential of clival masses as they can be the presenting symptom of distant malignancy.

Level of Evidence 4.

Keywords

- skull base
- clivus
- clival metastases
- clival tumor
- clival chordoma

Introduction

Tumors of the clivus are extremely rare. The clival chordoma and chondrosarcoma are the most common of these tumors; however, these each represent only 0.1 to 0.2% of all intracranial tumors.^{1,2} Metastatic lesions of the clivus occupy an even smaller subset of these tumors, with no more than 34 cases previously reported in the literature.³ Given the scarcity of metastatic clival lesions, this diagnosis is appropri-

ately low on the differential diagnosis of clival masses. We aim to update the current state of the literature since this was last evaluated by Pallini et al³ and to present two such cases, one of which occurred in the context of a patient with a history of prior clival chordoma resection. Additionally, this review seeks to identify unique characteristics of clival metastases that might help preoperatively distinguish these rare clival tumors from more common primary clival tumors.

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Fig. 1 Magnetic resonance imaging (MRI) of patient with a history of prior clival chordoma resection who presents with a new clival mass. The clival mass (white arrow) is isointense on T2-weighted axial (A) and coronal (B) images. T1-weighted coronal images demonstrate an isointense clival mass that enhances after gadolinium administration (C). Isointensity on T2-weighted images is atypical for chordomas; however, given the history, a transnasal transsphenoidal resection was undertaken. Final pathology was consistent with metastatic leiomyosarcoma, grade 2.

Case 1

A 62-year-old woman presented with a 1-month history of right posterior occipital headaches and a sharp stabbing sensation behind her left eye. Her past medical history was significant for a clival chordoma status posttranssphenoidal resection 5 years prior with 70 Gy postoperative radiotherapy over 7 weeks, as well as a lower extremity leiomyosarcoma with liver, lung, and bone (ulnar) metastases that had been stable for the last 2 years on the chemotherapeutic agent trabectedin, by stable leiomyosarcoma metastases. New-onset double vision brought her to the emergency room for evaluation. She was found to have a sixth nerve palsy, and magnetic resonance imaging (MRI) demonstrated a T1- and T2-isointense mass at the clivus measuring $3.3 \times 1.7 \times 1.1$ cm (**Fig. 1**). The patient was taken to the operating room for resection of this mass through an uncomplicated endoscopic transnasal transsphenoidal corridor. Pathology demonstrated a spindle cell neoplasm that stained positive for desmin, smooth muscle action (SMA), and a newer immunomarker, caldesmon. Caldesmon, a high molecular weight immunomarker, is predominantly expressed in thin (actin) filaments of smooth muscle cells. Thus all three immunomarkers were

supportive of metastatic leiomyosarcoma. The tumor stained negatively with pankeratin, epithelial membrane antigen (EMA), and S-100, which rules out the possibility of a chordoma (**Fig. 2**). At 7 months postoperatively, the patient remained alive with disease but was lost to follow-up.

Case 2

A 53-year-old woman with no significant past medical history presented with intermittent diplopia secondary to a right sixth cranial nerve palsy. She was otherwise completely asymptomatic. MRI showed a midclival T2-hyperintense, T1-isointense, and contrast-enhancing mass measuring $2.3 \times 2.2 \times 1.8$ cm (**Fig. 3**). The mass was eccentric to the right, abutted the right internal carotid, remodeled the inferolateral aspect of the sella turcica on the right, protruded through the posterior clival cortex, and bulged into the sphenoid sinus anteriorly. The patient was taken to the operating room and had a complete gross resection performed endoscopically through a transnasal transsphenoidal corridor. Pathology of this clival tumor demonstrated features of mucinous adenocarcinoma. This tumor stained with pankeratin, Cam5.2, carcinoembryonic antigen (CEA), and keratin

Fig. 2 Pathology from endoscopic transnasal transsphenoidal resection of a leiomyosarcoma clival metastasis. (A) Hematoxylin and eosin staining demonstrates a spindle cell neoplasm with moderately pleomorphic nuclei with mitotic figures. Immunohistochemistry was positive for desmin, smooth muscle action, and caldesmon as shown in figure (B) and negative for CKAE1/AE3, GFAP, Ki67, S100, EMA.

Fig. 3 Magnetic resonance imaging (MRI) of a patient with metastatic breast adenocarcinoma to the clivus. This clival metastasis (arrow) is hypointense on coronal cuts of a T1-weighted MRI (A) and enhances after administration of gadolinium (B). The mass demonstrates hyperintensity in this (C) axial T2-weighted MRI. Final pathology demonstrated metastatic mucinous adenocarcinoma of the breast.

7. It did not stain with S-100, which rules out the diagnosis of chordoma. The diagnosis of breast carcinoma was supported in addition by positive staining with mammaglobin and GCDFP15 (►Fig. 4). Postoperative positron emission tomography (PET) revealed no uptake in the grossly resected clival region but did reveal a breast lesion with axillary lymphadenopathy. Follow-up computed tomography (CT) demonstrated rib, thoracic vertebral body, and clavicular metastatic lesions, as well. Core biopsy of the breast revealed identical morphology and immunohistochemistry compared with the metastatic clival tumor. The patient is currently alive with stable metastatic disease after 5,040 cGy of intensity-modulated radiation therapy and is maintained on hormonal therapy.

Literature Review

A literature review of the MEDLINE database (1950 to January 19, 2013) was performed to identify all cases of patients with metastatic disease to the clivus. Most of the reports were case reports, small case series, or single cases that were part of larger case series discussing surgical

technique. In total, 47 cases were identified in the literature, including the two cases presented here. These findings are summarized in ►Table 1.^{3–37}

There is a preponderance of men reported with clival metastases (72.1%, 31/43), and the median age of these patients is 58 years with a wide range (3 to 83 years). Metastatic disease to the clivus was the initial presenting symptom of the primary malignancy in 36% of the cases that reported this information (13/36). When there was a history of malignancy, the median interval of time to clival metastases was 24 months (1 to 172 months). Clinical symptoms manifested often as single or multiple cranial neuropathies, with at least abducens palsies as the initial presenting symptom in 61.9% (26/42) of patients. Primary tumors arose from multiple sites, with the pelvis (25.5%, 12/47), abdomen (23.4%, 11/47), chest (19.1%, 9/27), and neck (10.6%, 5/47) as the most common sites. Tumor pathology was diverse, but several pathologies were seen more commonly: prostate carcinoma (18.1%, 9/47), hepatocellular carcinoma (10.6%, 5/47), and thyroid follicular carcinoma (8.5%, 4/47).

Reporting of radiographic findings was sparse. Often, reporting made mention of either only T1 or T2 sequences

Fig. 4 Pathology from endoscopic transnasal transsphenoidal resection of a breast mucinous adenocarcinoma clival metastasis. (A) Hematoxylin and eosin staining reveals nests of tumor separated by a richly vascularized abundant mucinous stroma. Immunohistochemistry staining demonstrated strong diffuse positivity for pankeratin (B), CAM5.2, CK7, mCEA, and synaptophysin and nonreactive with prolactin, chromogranin, CD56, S100, p62, CDX-2, CK 20, and CD117.

Table 1 Reported cases of clival metastases

Author	Year	Age	Gender	Pathology	Interval from primary tumor to clival metastasis (mo)	Signs and symptoms at time of clival metastasis			Follow-up (mo)	Condition
Turner, et al	1980	20	M	Ewing sarcoma	2	No	Yes	Fever, neck pain	NA	NA
Greenberg, et al	1981	58	M	Prostate CA	NA	Yes	No	None	NA	NA
Ruchti, et al	1987	71	F	Thyroid follicular CA	NA	No	No	Multiple CN palsies	NA	NA
Hirai, et al	1992	48	M	Gastric CA	0	Yes	No	None	5	DOD
O'Boyle, et al	1992	71	M	Prostate CA	0	Yes	No	Vision loss	NA	NA
Sim, et al	1994	40	M	Hepatocellular CA	1	No	No	Epistaxis	NA	NA
Casals, et al	1995	61	M	Thyroid follicular CA	0	No	No	Dysarthria, otalgia	15	AWD
Altman, et al	1997	81	M	Thyroid follicular CA	0	No	Yes	None	12	AWD
Kim, et al	1998	43	M	Hepatocellular CA	0	Yes	No	None	NA	NA
Kelley, et al	1999	74	M	Renal cell CA	NA	No	No	Multiple CN palsies	NA	NA
Salas, et al	1999	na	NA	CA, unspecified	NA	NA	NA	NA	10	DOD
Rosahl, et al	2000	50	F	Thyroid follicular CA	6	No	No	Multiple CN palsies	12	AWD
Escott	2001	56	F	Melanoma	24	NA	NA	NA	NA	NA
Endo, et al	2001	59	M	Renal cell CA	NA	No	Yes	XII CN palsy	6	DOD
Alessi, et al	2003	66	F	Leiomyoma	72	Yes	No	XII CN palsy	12	AWD
Kingdom, et al	2003	na	NA	Liposarcoma	NA	Yes	No	None	NA	NA
Kingdom, et al	2003	na	NA	Renal cell CA	NA	NA	NA	NA	NA	NA
Kingdom, et al	2003	na	NA	Adenocarcinoma, unspecified	NA	NA	NA	NA	NA	NA
Kocak, et al	2003	46	M	Lung, small cell CA	2	Yes	Yes	None	4	DOD
McDermott, et al	2004	54	M	Prostate CA	62	No	Yes	None	3	DOD
McDermott, et al	2004	68	M	Prostate CA	124	No	No	VII palsy	29	DOD
McDermott, et al	2004	58	M	Prostate CA	39	Yes	No	None	31	DOD
McDermott, et al	2004	67	M	Prostate CA	40	No	No	Visual loss	NA	NA
McGirt, et al	2005	3	M	Neuroblastoma	0	No	No	Visual loss	NA	NA
Ulubas, et al	2005	51	F	Lung, squamous cell CA	0	No	Yes	Back pain	1	DOD

(Continued)

Table 1 (Continued)

Author	Year	Age	Gender	Pathology	Interval from primary tumor to clival metastasis (mo)	Signs and symptoms at time of clival metastasis			Follow-up (mo)	Condition
Kim, et al	2006	50	F	Hepatocellular CA	NA	Yes	No	Multiple CN palsies	NA	NA
Isaka, et al	2006	19	M	Pulmonary, carcinoid	0	Yes	Yes	Cough	13	DOD
Malloy	2007	70	M	Prostate CA	3	Yes	No	None	24	AWD
Santarpia, et al	2008	23	F	Medullary thyroid CA	172	No	Yes	Hemianopsia, diabetes insipidus	2	DOD
Marchese, et al	2008	51	M	Tonsillar CA	14	Yes	Yes	None	4	DOD
Pallini, et al	2009	31	M	Melanoma	96	Yes	No	None	18	DOD
Pallini, et al	2009	67	F	Lung, adenocarcinoma	0	Yes	No	None	12	DOD
Pallini, et al	2009	69	M	Hepatocellular CA	0	Yes	No	Left facial pain, ptosis, anisocoria	3	AWD
Pallini, et al	2009	50	M	Prostate CA	0	Yes	No	None	6	AWD
Pallini, et al	2009	57	M	Lung, squamous cell CA	24	Yes	Yes	None	12	AWD
Pallini, et al	2009	76	M	Squamous cell CA	12	Yes	No	Asthenia, anorexia	14	AWD
Pallini, et al	2009	70	M	Prostate CA	120	Yes	No	None	3	AWD
Barriere, et al	2009	57	M	Rectal, GIST	0	Yes	Yes	Diplopia	17	DOD
Fraser, et al	2010	72	M	CA, unspecified	NA	No	No	None	NA	NA
Nozaki, et al	2010	65	M	Hepatocellular CA	7	Yes	Yes	Multiple CN palsies	12	AWD
Kolias, et al	2010	64	M	Prostate adenocarcinoma	0	Yes	No	Multiple CN palsies	17	DOD
Baeg, et al	2010	70	M	Gastric, GIST	0	Yes	No	None	3	AWD
Ng, et al	2011	83	F	Breast, ductal CA	11	No	Yes	Ptosis, ophthalmoplegia	NA	NA
Bohnstedt, et al	2012	14	F	Myoepithelial CA	12	Yes	No	None	12	DOD
Fukushima, et al	2012	64	M	Gastric, signet ring cell CA	120	Yes	Yes	None	10	AWD
UCLA	2013	52	F	Breast adenocarcinoma	0	Yes	No	VI palsy	19	AWD
UCLA	2013	62	M	Leiomyosarcoma	48	Yes	No	VI palsy	7	AWD

Abbreviations: AWD, alive with disease; CA, carcinoma; CN, cranial nerve; DOD, dead of disease; GIST, gastrointestinal stromal tumor; NA, not available.

or no mention at all. Only 14 cases made mention of gadolinium-enhancement, and all confirmed either heterogeneous or strongly enhancing clival masses. Similarly, only 11 reports of T1 findings were available, and metastases presented with the complete range of T1 findings including hypointensity, hyperintensity, and isointensity. Only seven reports were available for T2 findings and similarly ranged from hypointense, hyperintense, or isointense on this sequence.

Discussion

The diagnosis of metastatic disease of the clivus is a challenge prior to surgical intervention. Clival metastases are extremely rare, with the last review of the literature only identifying 34 cases in 2009.³ Our current report and literature review identified an additional 13 cases to update the total to 47 reported cases of clival metastases in the world literature. Additionally, reports of clival metastatic disease are accelerating. In the 1980s only three cases were reported, whereas there were eight cases in the 1990s, 27 in the 2000s, and an additional 9 in the first 3 years of the current decade (see ►Table 1). This may be due to several factors, including increased awareness of this pathology, less morbid surgical interventions with the introduction of endoscopic endonasal approaches to the clivus, and increasing longevity of patients with metastatic disease.

Clival metastases are likely to share the same pathophysiology of the more common spinal metastasis. Hematogenous spread of cancer cells is extremely complex and not fully understood, but in part requires venous or arterial access to the bony site.³⁸ Venous access to the clivus can occur via two routes. During Valsalva, venous blood bypasses the caval system and is shunted through the Batson plexus into the internal vertebral venous plexus system, which communicates superiorly with the basilar plexus at the clivus. Therefore, once intra-abdominal, thoracic, and pelvic tumor metastases have reached the internal vertebral venous plexuses, these cells are driven superiorly during Valsalva.³⁹ Similarly, the basilar plexus communicates with the bilateral inferior petrosal sinuses, which drain the cavernous sinuses. Hematogenous spread of infection from the orbits, sinuses, and face can similarly shunt venous drainage into the cavernous sinus via the inferior ophthalmic vein,⁴⁰ subsequently accessing the clivus. The pathology represented in this literature review may in part be a reflection of the venous access to the clivus from anatomic sites in the pelvis (25.5%, 12/47), abdomen (23.4%, 11/47), chest (19.1%, 9/27), and neck (10.6%, 5/47).

We report two cases that highlight some of the diagnostic dilemmas presented by clival metastatic lesions. One of the cases involved a patient with no history of malignancy, and it was not until final pathology demonstrated breast cancer that further work-up identified the primary tumor. This is not an uncommon presentation of clival metastases and represents 36% of the reported cases in the literature. In patients with a known history of malignancy, over half the clival metastases presented more than 2 years from the treatment of the original malignancy and the upper limit was well over

10 years. Therefore, even a remote history of malignancy can develop a late hematogenous metastasis to the clivus. In the other case presented in this review, a clinical history of a previously resected clival chordoma obfuscated the patient's history of leiomyosarcoma. Metastasis to a previously operated clivus for a chordoma is a novel case that highlights the high level of suspicion required when approaching a clival lesion.

The differential diagnosis for tumors of a clival mass includes chordoma, chondrosarcoma, plasmacytoma, and clival metastases.⁴¹ MRI can be used to help differentiate these preoperatively, but this is not entirely reliable, as illustrated by the wide range of MRI findings in our literature review, as well as our first case. The first case presented had MRI findings consistent with a clival chordoma and a chondrosarcoma. Specifically, these pathologies and Case 1 demonstrated MRI findings consistent with destructive bone lesions with isointensity or hypointensity T1-weighted images, hyperintensity on T2-weighted imaging, and enhancement with gadolinium.⁴² Plasmacytomas can be hyperintense on T1-weighted images and enhance with gadolinium,⁴¹ but two cases in the literature demonstrate T1 hyperintensity of clival metastases, as well.^{15,23} The reported radiographic findings in the literature on clival metastases demonstrate a wide array of T1 and T2 intensities. As is seen in chordomas and chondrosarcomas, there is no characteristic intensity on T1 or T2 imaging, though all reported cases do enhance with gadolinium. An atypical finding on MRI should raise a flag that the differential may need to be broadened.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) and radionuclide bone scans are commonly used in staging and surveillance for a variety of malignancies,⁴³ but due to the rare nature of primary clival tumors there is not a well-defined role for FDG-PET or radionuclide bone scans. Radionuclide bone scans have been used historically to identify osteoblastic processes within the skeleton, such as metastatic lesions. Additionally, chordomas and chondrosarcomas follow indolent locally destructive clinical courses with little metastatic potential.⁴⁴ However, in the case of clival metastases, FDG-PET has the potential to be an important adjunct to identifying an unknown primary or progression of a prior tumor. A discussion of the difference between bone scans and FDG-PET is beyond the scope of this report; however, it should be noted that FDG-PET imaging does include the viscera (as opposed to just the skeletal system) and thus could serve as a better means by which to identify a silent primary or a previously dormant tumor. Only two of the clival metastasis reports identified describe FDG-PET findings,^{6,28} and seven reported bone scan findings.^{10,14,16,21,27,31,36} Nozaki et al²⁸ report a patient that had a previously embolized hepatocellular carcinoma 7 months prior to presenting with multiple cranial neuropathies. FDG-PET demonstrated no uptake in the liver but did show uptake in the clivus. Baeg et al,⁶ report a patient presenting with diplopia secondary to a clival mass. FDG-PET imaging was only obtained after emergent debulking but did identify a new gastric tumor. In Case 2, the postoperative FDG-PET scan identified a previously asymptomatic breast

tumor and the postoperative scan demonstrated no activity in the clivus, possibly due to resection of the metastasis. These two cases in the literature, as well as our cases presented in here, illustrate the role of FDG-PET in evaluation of clival metastases: postoperative identification of an unknown primary and preoperative evaluation of a clinically distant known primary.

The clivus occupies a critical anatomic region just anterior to the brainstem, and though clival pathology can result in dramatic clinical findings, these findings are nonspecific. Tumor growth in this location quickly impacts cranial nerves and is demonstrated in the presenting signs and symptoms in ►Table 1. Specifically, the sixth cranial nerve is extremely vulnerable to injury from clival tumors because of its long tortuous path from the brainstem to the superior orbital fissure. The nerve exits the pontomedullary junction and then enters into an osteofibrous conduit formed by the petrous apex and the petrosphenoidal ligament, the Dorello canal. Throughout its course it takes three separate turns where it is tightly adherent, exposing it to injury.⁴⁵ In a review of the literature of clival metastases, 64.3% (27/42) of the patients with clival disease presented with at least an abducens cranial nerve palsy. This by no means differentiates clival metastases, but it does highlight the ominous nature of an abducens palsy. A review of 48 patients with chordoma and 49 patients with low-grade chondrosarcoma of the skull base reported abducens nerve palsy occurring in 46% of patients with chordoma and 47% of patients with chondrosarcoma.⁴⁶

There is a preponderance of men reported with clival metastases (72.1%, 31/43), and the median age of such patients is 58 years with a wide range (3 to 83 years). This is not unique, and again is consistent with chordoma findings reported in a population-based study using the Surveillance, Epidemiology, and End Results (SEER) database with a predominance in men and peak age between 50 and 60 years of age.⁴⁷ Clival chondrosarcomas tend to occur a decade earlier, with case series reporting between 30 and 50 years of age and a more even gender distribution.^{1,46,48}

Conclusion

To date, there have been only 47 previously reported cases of metastatic disease to the clivus in the literature. Although clival metastases are extremely rare, they are an important part of the differential diagnosis of clival masses. Clival metastases can occur in the context of a known history of a distant malignancy; however, clival metastases can be the presenting symptom of a distant malignancy and must be maintained in the differential diagnosis regardless of past medical history.

Note

This study was presented as a poster presentation at the North American Skull Base Society Annual Meeting, February 17 to 19, 2012, Las Vegas, NV.

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