

# Periampullary Carcinoma: Unusual Sites of Metastasis

Anju Bansal, MD, Varsha Dalal, MD, Manveen Kaur, MD, Fouzia Siraj, DNB

National Institute of Pathology, Indian Council of Medical Research, Safdarjung Hospital, New Delhi, India

**Background:** Periampullary neoplasms include carcinomas of the duodenum, ampulla of Vater, distal common bile duct, and pancreas. The aggressive course of these neoplasms is attributable to the delay in diagnosis, as patients have no symptoms until advanced stages of the disease. More than half of patients have distant metastasis at the time of diagnosis. The most frequent sites of metastasis are the liver, lymph nodes, peritoneum, lung, bone, kidney, and, rarely the skin.

**Case Report:** We report the case of a 45-year-old female patient with adenocarcinoma of the ampulla of Vater metastasizing to the right parietal skull with overlying cutaneous involvement 1 year after a Whipple procedure.

**Conclusion:** Cutaneous and skull metastasis of periampullary neoplasms is unusual, but early recognition of such metastatic disease is important because it indicates a poor prognosis for the patient.

**Keywords:** Ampulla of Vater, neoplasm metastasis, skull

Address correspondence to Anju Bansal, MD, National Institute of Pathology, Indian Council of Medical Research, Safdarjung Hospital, New Delhi 110029, India. Tel: +91-981-036-8354. Email: dranjubansal@yahoo.com

## INTRODUCTION

Periampullary neoplasms include carcinomas of the ampulla of Vater, distal common bile duct (CBD), pancreas, and duodenum.<sup>1,2</sup> Carcinoma of the ampulla of Vater is an uncommon tumor that accounts for approximately 0.2% of all gastrointestinal malignancies with an estimated incidence of <6 cases per 1,000,000 population per year.<sup>3</sup> The liver is the predominant site of metastatic disease, followed by the lymph nodes, peritoneum, lung, bone, kidney, and rarely, the skin. Skull metastases with overlying cutaneous involvement have rarely been reported.<sup>3</sup> We describe the radiologic and morphologic findings of our patient and present a brief review of the literature.

## CASE REPORT

A 45-year-old female presented with a swelling on the forehead that began 3 months earlier (Figure 1). The swelling had progressively increased in size and was associated with a dull, deep-seated headache for the past month. The patient had no history of trauma. During examination, the swelling measured 5 × 5 cm and was hard on palpation. The skin over the swelling was tense and could not be pinched. The patient showed no signs of neurologic impairment. A clinical diagnosis of appendageal tumor was made, and the patient was referred for radiologic examination and biopsy.

Magnetic resonance imaging (MRI) and computed tomography (CT) scans revealed an expansile osteolytic calvarial lesion in the left parietal region expanding to the midline (Figure 2). No other lesions were noted within the brain or dura mater. The histopathologic examination of the Tru-Cut biopsy of the swelling showed a fragmented

skin biopsy with several nests and sheets of atypical epithelial cells with a high nucleocytoplasmic ratio and marked nuclear pleomorphism in the dermis (Figure 3). Occasional gland formation was also seen (Figure 4A). With a provisional diagnosis of metastatic adenocarcinoma, immunohistochemistry (IHC) was performed for the most common sites of primary malignancy metastasizing to the skull and revealed positivity for cytokeratin (CK) 7, carcinoembryonic antigen, and epithelial membrane antigen and negativity for CK20 in the tumor cells (Figure 4B). The patient's records revealed that she had undergone a Whipple operation for an adenocarcinoma of the ampulla of Vater 1 year earlier, followed by chemotherapy (Figure 5). The histopathology report documented infiltration of the duodenal wall, pancreas, and 3 peripancreatic lymph nodes by the tumor. The resection margins, however, were free.

The adenocarcinoma of the ampulla of Vater was staged as IIB per tumor node metastasis (TNM) staging (pT3 N1 M0 R0), and the patient was administered chemotherapy with gemcitabine. The dosage was 1,000 mg/m<sup>2</sup> on days 1, 8, and 15. The cycle was repeated every 4 weeks from day 1, and the patient completed 4 cycles. She responded well to the treatment but was lost to follow-up after 6 months. The morphologic picture and IHC profile of the forehead swelling confirmed the diagnosis of cutaneous and skull metastases from the adenocarcinoma in the ampulla of Vater.

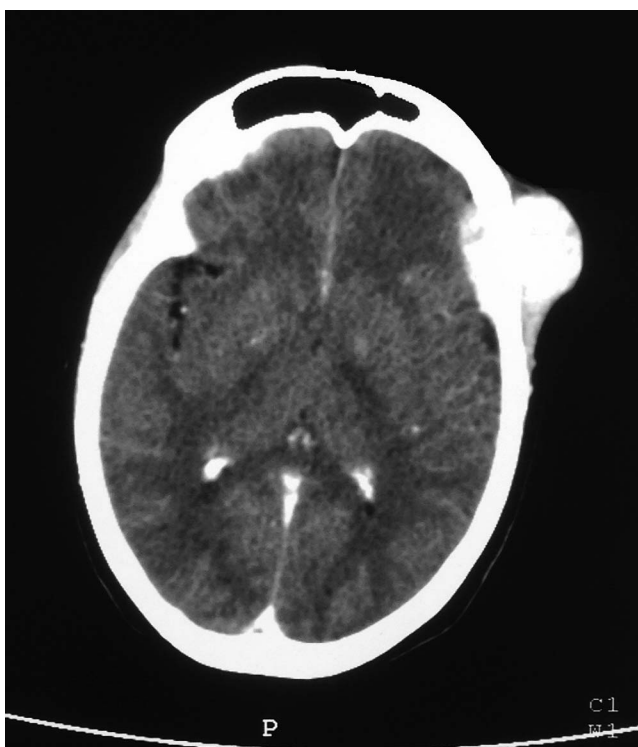
## DISCUSSION

The ampulla of Vater is a complex region where the CBD and the main pancreatic duct converge to enter the second portion of the duodenum in the vicinity of the pancreatic

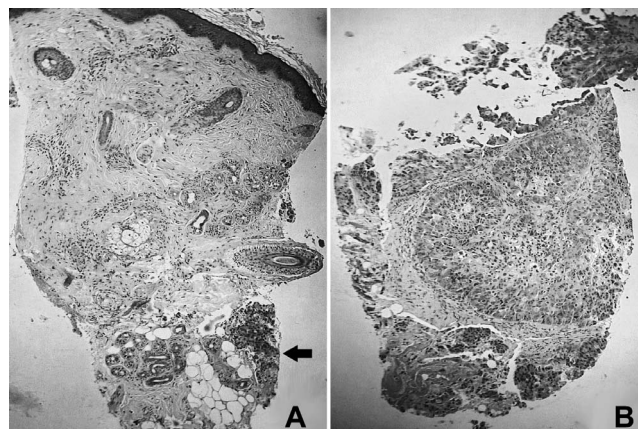


**Figure 1.** Clinical photograph of the patient shows a progressively increasing swelling on the forehead that was hard on palpation.

head. The term periampullary encompasses any of the 4 elements that form this region, ie, the CBD, pancreas, ampulla, and duodenum. Carcinoma of the ampulla of Vater is the second most common malignancy in the periampullary region after carcinoma of the pancreas. Peak incidence is in the 7th and 8th decades of life with a slight male preponderance.<sup>4</sup> Our patient, however, was a middle-aged female. The usual presentation of ampullary tumors is biliary



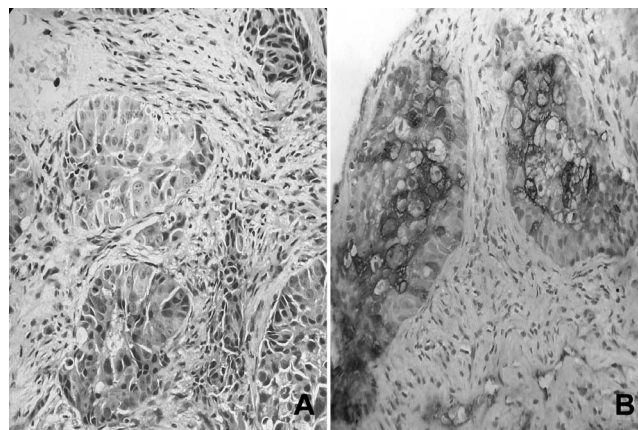
**Figure 2.** Computed tomography scan reveals expansile osteolytic calvarial lesion in the left parietal region expanding to the midline.



**Figure 3.** A: Fragmented skin biopsy shows nests and sheets of atypical epithelial cells (arrow) in the mid and deep dermis (hematoxylin and eosin [H&E] 100 $\times$ ). B: Microphotograph shows atypical epithelial cells arranged in sheets and nests with occasional lumina (H&E 100 $\times$ ).

obstruction: obstructive jaundice, right upper quadrant pain, and weight loss. Distant metastatic disease most frequently involves the liver, lymph nodes, peritoneum, lungs, bone, kidney, and, rarely the skin.<sup>5</sup> An extensive search of the literature revealed 2 cases of skull and 2 cases of cutaneous metastases of ampullary carcinoma (Table).<sup>3,5-7</sup>

Metastases of the skull are classified into 2 anatomic groups with distinct clinical features. One is calvarial metastasis, which is usually asymptomatic, as in our case, but may cause dural invasion, dural sinus occlusion leading to meningeal irritation, and focal neurologic signs and other cosmetic problems. Skull-base metastases, on the other hand, usually cause various combinations of cranial nerve signs and syndromes. Breast cancer is the most frequent source of skull metastases, followed by lung, thyroid, and renal cell carcinoma and malignant melanoma.<sup>8-10</sup>



**Figure 4.** A: Microphotograph shows occasional gland formation by tumor cells. The tumor cells show moderate pleomorphism. Single cell infiltration is also noted (hematoxylin and eosin 200 $\times$ ). B: Immunohistochemistry for carcinoembryonic antigen revealed membranous positivity in tumor cells (200 $\times$ ).





**Figure 5.** Microphotograph shows the 101 × 113-mm tumor in the ampulla of Vater with histopathologic features of adenocarcinoma (hematoxylin and eosin 200×).

MRI is the best method to detect skull metastases, which appear as focal lesions of low-intensity signal on precontrast T1-weighted images. A contrast-enhanced fat-saturated sequence is important to demarcate the lesions in bone marrow fat. MRI demonstrates tumor invasion into the dura mater, brain surface, or cranial nerves better than any other imaging modality. On x-ray film and CT scan, calvarial metastases appear as focal osteolytic or osteoblastic lesions of both the inner and the outer table of the calvaria. Radionuclide bone studies are valuable screening tests to detect bone metastases.<sup>8</sup>

Skin metastasis is an uncommon event that occurs in 0.7%-9.0% of all patients with cancer.<sup>11</sup> When present, skin metastasis signifies disseminated disease and grim prognosis. These lesions may appear nodular, inflammatory, or

sclerodermoid. Subcutaneous or dermal nodules that are rapidly growing, are stony hard, and have associated pain/tenderness and ulceration strongly favor a possibility of skin metastases. The distribution of skin metastases is related to both the location of the primary malignancy and the method of spread. Women with skin metastases have the following distribution in decreasing order of frequency of primary malignancies: breast, ovary, oral cavity, lung, and large intestine.<sup>7,11</sup> Periampullary carcinomas with cutaneous metastases are rare; to our knowledge only 2 cases have been reported in the literature.<sup>5,7</sup>

Intestinal and pancreaticobiliary types represent the most common histologic subtypes, indicating that periampullary carcinomas emanate from the corresponding epithelia covering the distal parts of the pancreas, CBD, and periampullary duodenum, respectively.<sup>2</sup> A more favorable prognosis has been observed for the intestinal subtype compared to the pancreaticobiliary subtype in some series.<sup>4</sup> Other histologic subtypes less commonly seen in an ampullary location include mucinous, signet-ring cell, neuroendocrine, and undifferentiated carcinomas.<sup>4</sup> Important prognostic variables include lymphovascular invasion, TNM stage, absence of nodal metastases, small primary size, well-differentiated tumors, absence of perineural invasion, T1-2 disease, and negative surgical resection margins. R0 resection—complete surgical resection of the tumor at the microscopic level—offers the only chance of cure; however, more than half of patients die of recurrence after R0 resection.<sup>3,4</sup>

Irradiation is an effective first-line therapy for patients with skull and cutaneous metastases. Chemotherapy or hormonal therapy is applied depending on tumor sensitivity. Bone resorption inhibitory drugs are used as a part of systemic therapy and should be studied for prevention of symptomatic skull metastasis. Surgery is indicated in patients who require immediate decompression, cosmetic recovery, or histologic diagnosis. Patients are selected on the basis of their clinical and functional status.<sup>3,6,8,9</sup>

Ampullary carcinomas generally have a better prognosis than cancers of the pancreas, with overall survival after 5 years of 84% in stage I, 70% in stage II, 27% in stage III, and 0% in stage IV per TNM staging. The aggressive course of these ampullary tumors is attributable to the delay in diagnosis, as patients have no symptoms until the ad-

**Table. Metastases After Whipple Procedure Reported in the Literature**

Author, Date	Age/Sex	Tumor Stage	Surgery Performed	Site of Metastases	Duration of Relapse Since Primary Diagnosis
Hopf et al, 2009 <sup>3</sup>	54/F	T2 N0 M0 R0	Pylorus-preserving Whipple	Right frontal: calvarial	5 years
Lamarca et al, 2012 <sup>5</sup>	72/M	T2 N1 M0 R0	Whipple	Cervical and thoracic region: cutaneous	18 months
Jeon et al, 2004 <sup>6</sup>	65/M	T2 N1 M0 R0	Whipple	Right parietal: calvarial	2 years
Cho et al, 2007 <sup>7</sup>	71/M	T2 N0 M0 R0	Pylorus-preserving Whipple	Acral skin and bone	27 months
Present case	45/F	T2 N1 M0 R0	Whipple	Left parietal: cutaneous and calvarial	1 year

F, female; M, male.

vanced stages of the disease.<sup>5</sup> Our case stands out because our patient was relatively young, experienced faster relapse than usual, and had a rare site of metastasis of periampullary carcinoma to the skull and overlying skin. Early recognition of such metastatic disease is paramount, as these sites are easily accessible for investigation and indicate poor prognosis and decreased survival for the patient.

## CONCLUSION

Periampullary adenocarcinomas are rare malignancies with an aggressive course of disease. Our patient presented with unusual sites of metastases of ampullary carcinoma 1 year after undergoing a Whipple procedure, followed by chemotherapy. To our knowledge, ours is the first report of metastasis to the skull with overlying cutaneous involvement of an ampullary adenocarcinoma.

## ACKNOWLEDGMENTS

*The authors have no financial or proprietary interest in the subject matter of this article.*

## REFERENCES

1. Aksoy M, Sumer A, Sari S, Mete O, Salmaslioglu A, Erbil Y. Pancreatic ampullary carcinoma with neck metastases: a case report. *Cases J*. 2009;2:146. doi: 10.1186/1757-1626-2-146.
2. Berberat PO, Künzli BM, Gulbinas A, et al. An audit of outcomes of a series of periampullary carcinomas. *Eur J Surg Oncol*. 2009; 35(3):187-191. doi: 10.1016/j.ejso.2008.01.030.
3. Hopf S, Buchalla R, Scheil F, Heusermann U, Börm W. Skull metastasis of ampulla of Vater adenocarcinoma 5 years after Whipple operation: case report and literature review. *J Neurooncol*. 2009;95:141-145. doi: 0.1007/s11060-009-9906-4.
4. Voutsadakis IA, Doumas S, Tsapakidis K, Papagianni M, Papandreou CN. Bone and brain metastases from ampullary adenocarcinoma. *World J Gastroenterol*. 2009 Jun 7;15(21): 2665-2668. doi: 10.3748/wjg.15.2665.
5. Lamarca A, Martinez-Marin V, Feliu J. Cutaneous relapse of an ampullary carcinoma: an unusual presentation. *BMJ Case Rep*. 2012 Jul 3;2012. doi:10.1136/bcr.01.2012.5580.
6. Jeon JY, Yi HJ, Lee SR, Paik SS, Lee KS. Skull metastasis from ampulla of Vater adenocarcinoma: case report. *J Neurooncol*. 2004 Mar-Apr;67(1-2):107-113.
7. Cho EY, Kim TH, Park SD, et al. Acral metastasis in a patient with ampullary carcinoma. *Korean J Intern Med*. 2007 Mar;22(1): 55-58. doi: 10.3904/kjim.2007.22.1.55.
8. Mitsuya K, Nakasu Y, Horiguchi S, et al. Metastatic skull tumors: MRI features and a new conventional classification. *J Neurooncol*. 2011 Aug;104(1):239-245. doi: 10.1007/s11060-010-0465-5.
9. Mitsuya K, Nakasu Y. Metastatic Skull Tumours: Diagnosis and Management. *European Association of NeuroOncology Magazine*. 2014;4(2):71-74.
10. Bansal A, Kaur M, Narula V. Cutaneous and bone metastasis of follicular thyroid carcinoma: a case report. *Tumori*. 2015 Jul 8:0. doi: 10.5301/tj.5000374.
11. Hussein MR. Skin metastasis: a pathologist's perspective. *J Cutan Pathol*. 2014 Sep;37(9): e1-e20. doi: 10.1111/j.1600-0560.2009.01469.x.

*This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.*