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CASE REPORT

Unusual presentation of metastatic hepatocellular carcinoma in the nasal septum: a case report and review of the literature

Ching-Wei Chang · Tsang-En Wang · Li-Tzong Chen · Wen-Hsiung Chang · Yi-Shing Leu · Yang-Kai Fan · Yu-Jan Chan

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Abstract Hepatocellular carcinoma with sinonasal metastasis is extremely rare. We report a case of a 49-year-old man who had a history of synchronous hepatocellular carcinoma and verrucous carcinoma of tongue. A painless and non-bleeding mass was found in the left nasal septum 16 months after hepatocellular carcinoma was diagnosed. On computed tomography, the mass was enhanced with contrast. It was resected and proved to be metastatic hepatocellular carcinoma. The patient was treated with radiotherapy to the nasal area and then with chemotherapy. He was still alive, 15 months after the appearance of the nasal metastasis.

C.-W. Chang · T.-E. Wang (✉) · W.-H. Chang
Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Mackay Medicine, Nursing and Management College, No. 92, Sec. 2, Chung Shan North Road, Taipei, Taiwan
e-mail: tewang@ms2.mmh.org.tw

L.-T. Chen
National Institute of Cancer Research, National Health Research Institutes, Taipei, Taiwan

L.-T. Chen
Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Y.-S. Leu
Department of Otolaryngology, Mackay Memorial Hospital, Taipei, Taiwan

Y.-K. Fan
Department of Radiology, Mackay Memorial Hospital, Taipei, Taiwan

Y.-J. Chan
Department of Pathology, Mackay Memorial Hospital, Taipei, Taiwan

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Introduction

Extrahepatic metastasis of hepatocellular carcinoma (HCC) is not uncommon in the late stage of the disease. It is reported in 14.0%–36.7% of patients [1, 2]. In an autopsy series of 232 cases, such lesions were present in about 50% [3]. The most frequent sites are abdominal lymph nodes, lung, bone, and adrenal gland [1, 3]. Metastasis to the nasal cavity and paranasal sinuses, however, has seldom been reported. We present such a case that was further complicated by a synchronous head and neck tumor.

Case report

A 49-year-old man who habitually used alcohol, cigarettes, and betel nut presented with a left tongue mass and a palpable right upper quadrant abdominal mass. He had no superficial lymphadenopathy. His serum HBsAg was positive and the alpha-fetoprotein level was 629,000 ng/ml. Dynamic computed tomography (CT) of the abdomen showed a diffuse, infiltrating, hypervascular liver tumor invading the portal vein and entirely consistent with a diagnosis of HCC. The chest film had several nodules suggestive of metastases. The tongue lesion was removed by partial glossectomy and proved to be a T1N0M0 verrucous carcinoma. The HCC was treated with radiotherapy to the liver and oral thalidomide. About 16 months later, a painless non-bleeding mass was found in the left nasal

Fig. 1 Mass in the nasal septum (arrow)

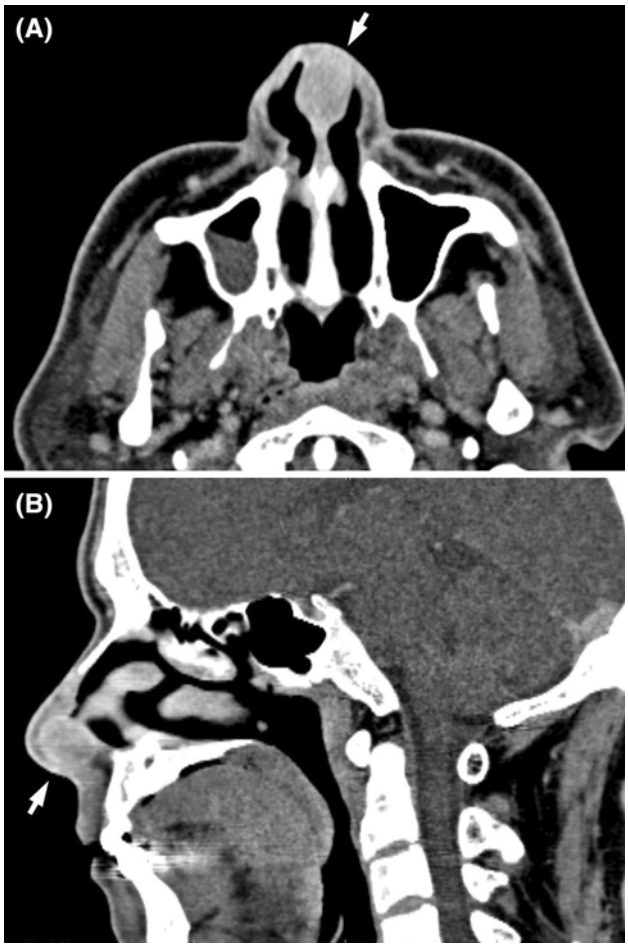

Fig. 2 Transverse (**a**) and sagittal (**b**) contrast-enhanced computed tomography of paranasal sinuses showing a 1.6 × 1.8-cm enhancing lesion in the nasal septum (arrows)

septum (Fig. 1). The pulmonary metastases were larger than before and the alpha-fetoprotein level, which had dropped with initial treatment, had again increased.

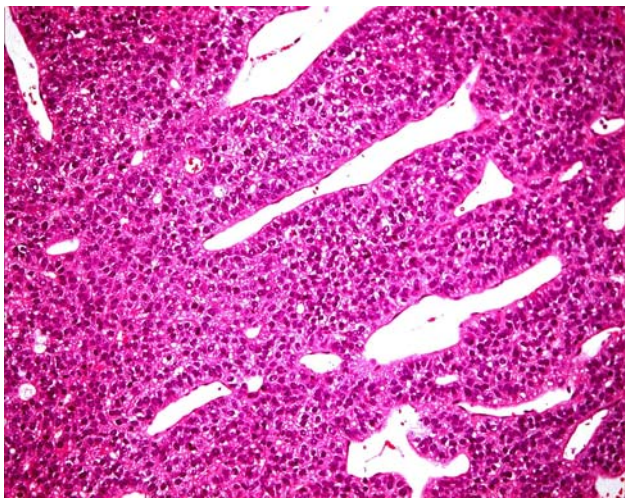

Fig. 3 Histologic section of the nasal lesion revealing neoplastic polygonal cells arranged in a thick trabecular pattern, consistent with metastatic hepatocellular carcinoma (H&E stain; magnification ×100)

Paranasal sinus CT showed an enhancing tumor in the nasal septum (Fig. 2a and b). Histologic examination of the subsequently resected mass revealed neoplastic, polygonal cells arranged in a thick trabecular pattern, consistent with metastatic HCC (Fig. 3). The patient was treated with adjuvant radiotherapy to the nose and was begun on systemic chemotherapy with oxaliplatin, fluorouracil, and leucovorin, resulting in partial remission of the pulmonary metastases. He was alive at 15 months after diagnosis of the nasal metastasis.

Discussion

Reports of HCC metastasis to the head and neck, including the jaw, orbital cavity, and skull are not unusual [4]. However, paranasal and nasal metastases from HCC are exceedingly rare. We were able to find only 17 such reports in the literature in the past 20 years (Table 1). All the patients were men, with ages ranging from 40 to 82 years old (mean 55.5). Although the etiology was not clear in all reports, seven patients had hepatitis B virus infection, one was hepatitis C infection, and two were alcohol abusers. The metastases were in both sinuses and nasal cavity in four cases, in the paranasal sinuses alone in eight, and in the nasal cavity alone in six.

Epistaxis was the most common symptom. Other less frequently reported symptoms included diplopia, gingival bleeding, nasal obstruction, proptosis, headache, and cheek pain according to the site of the tumor involved. However, these symptoms and signs are identical to those that may be produced by primary head and neck tumors, and there are

Table 1 Clinical features in 18 men with hepatocellular carcinoma metastatic to the sinonasal area

References	Age (years)	Possible etiology	Symptoms/Signs	Anatomic locations	Survival after diagnosis
[5]	42	Hepatitis B	Diplopia	Sphenoid sinus	Still alive after 6 months
	42	Hepatitis B	Epistaxis	Maxillary sinus	Died of hepatic failure after 3 months
[6]	71	Non-B non-C carrier	Epistaxis	Maxillary sinus and nasal cavity	Died of liver failure after 8 weeks
[7]	64	Hepatitis B	Epistaxis	Nasal cavity	Unknown
[8]	50	Hepatitis B	Epistaxis	Right nasal cavity	Unknown
[9]	67	Hepatitis C	Gingival bleeding	Maxillary sinus	Metastasis found at autopsy
[4]	45	Hepatitis B	Nasal septal granular mass	Nasal septum	Died of hepatic failure after 6 weeks
[10]	59	Unknown	Diplopia	Sphenoid sinus	Unknown
[11]	59	Hepatitis B	Epistaxis and nasal obstruction	Left maxillary sinus and nasal cavity	Died of hepatic failure
[12]	44	Immunosuppressive therapy	Epistaxis	Maxillary sinus and nasal cavity	Unknown
[13]	50	Unknown	Epistaxis and nasal obstruction	Left nasal cavity	Unknown
[14]	40	Unknown	Epistaxis	Sphenoid sinus	Unknown
[15]	67	Unknown	Proptosis	Sphenoid sinus	Died of hepatic failure after 21 months
	40	Unknown	Headache, left cheek pain	Left ethmoid sinus	Died of hepatic coma after 1 month
	67	Unknown	Left exophthalmos	Left frontal sinus	Unknown
[16]	82	Unknown	Epistaxis	Maxillary and ethmoid sinus with extension to nasal cavity	Died of hepatic failure
[17]	61	Alcohol	Epistaxis	Left nasal cavity	Died of respiratory failure after 2 months
Present report, 2007	49	Hepatitis B and alcohol	Nasal septal mass	Left nasal cavity	Still alive after 15 months

no distinctive clinical or radiologic features that can easily separate primary from metastatic lesions [18, 19]. The only clue might be a history of a primary tumor elsewhere, for example, in a patient with a history of HCC. A confusing factor in our patient's case, of course, was the history of two primary lesions, HCC and a verrucous carcinoma of the tongue.

Verrucous carcinoma is a well-differentiated squamous cell carcinoma that usually has a good prognosis. Complete resection is the treatment of choice, which was done in our patient. Distant metastasis of verrucous carcinoma is rare, but local recurrence following surgery is not uncommon [20, 21]. In addition, patients with one squamous cell carcinoma of the head and neck not infrequently develop a second primary malignancy in the upper aerodigestive tract [22]. In our patient, therefore, the nasal mass seemed most likely to be a recurrence of his verrucous carcinoma or a second primary head and neck tumor. It was only on biopsy that the true diagnosis was revealed.

As diagnosis and treatment of HCC have improved, patients are surviving longer, so it's perhaps not surprising that they are living long enough for extrahepatic metastases to become apparent [23, 24]. Thalidomide is effective in slowing progression of HCC in some cases [25], and this treatment may be what permitted our patient to survive long enough to develop this unusual metastasis. It's also interesting to note that of the 17 published reports of HCC metastatic to sinonasal region, 10 have been published in the past 7 years (Table 1), and ours makes the 11th. The numbers are too small to draw accurate statistical conclusions, but one wonders if we will continue to see more such reports as these people survive longer.

In most reported series of HCC, the male-to-female ratio ranges from 2:1 to 8:1 [26, 27]. The tumors in women tend to have less aggressive characteristics than in men, such as smaller mean tumor size, less advanced Okuda stage, and less frequent portal or hepatic vein invasion [27]. It is, therefore, intriguing to note that all reported cases of HCC metastatic to the sinonasal area have been in men. While

the exact reasons for the unequal gender distribution is unclear, investigators have postulated that differences in DNA synthetic activity and sex hormones may contribute to it at least in part [28]. Studies from animal models suggest that the hormonal effect may be related to testosterone's ability to enhance transforming growth factor alpha-related hepatocarcinogenesis and hepatocyte proliferation [29]. In addition, men may have a higher incidence of HBV infection and cirrhosis and differences in lifestyle, such as heavy alcohol consumption and smoking, that contribute to their increased risk [30, 31].

HCC metastasizes by either lymphogenous or hematogenous spread [32]. The former would involve invasion via the hepatic lymph nodes into the thoracic duct. In such a case, hepatic, peripancreatic, celiac, and paraaortic lymph nodes would be expected to be invaded before the disease would spread into the head and neck [33]. This does not fit with the finding of an isolated metastatic nasal or paranasal metastasis. Several hematogenous routes have been suggested [18, 19, 32]. The most conventional proposal is spread from the caval venous system through the pulmonary circulation and then into arterial vessels feeding the head and neck. Another possibility is retrograde spread through the prevertebral and vertebral venous plexus [18]. Such routes could also explain renal, bronchogenic, breast, and urogenital cacinomas metastases in the paranasal sinuses [19]. In our patient, there was no neck lymphadenopathy, but he did have lung metastases, so it seems more likely the nasal tumor arrived hematogenously. Lin [4] and Matsuda [6] also proposed this route for HCC metastatic to the nasal cavity.

Extrahepatic metastasis is a major independent predictor of a poor outcome in patients with HCC [34, 35], particularly with head and neck metastases [36]. In the published reports we reviewed, the survival (when stated) ranged from 6 weeks to 21 months after the appearance of sinonasal metastasis. Various treatments for the metastatic lesions were reported, including resection, palliative radiotherapy, and transcatheter embolization to control nasal bleeding. With resection of the nasal mass, adjuvant radiotherapy to the nose, and systemic chemotherapy, our patient was still alive 15 months after the appearance of the nasal metastasis.

It is fortunate that this patient's metastatic lesion was so easy to diagnose by biopsy, as it could not be differentiated clinically from a recurrent verrucous carcinoma or a second primary squamous cell carcinoma. This case is a good reminder that, while our differential diagnosis for a particular patient is often based on probability, it is merely a guide to our diagnostic approach. We still need tissue to make a definitive diagnosis, one which occasionally surprises us.

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