Abstract. We describe the palliative therapy for multiple metachronous oral metastases of hepatocellular carcinoma in a 72-year-old patient with emphasis on maintaining oral functions by local debulking procedures in due consideration of the dissemination of the neoplasm to multiple organs. The first oral metastasis was the first evidence of multiple tumor spread after partial hepatectomy. Palliative chemotherapy with sorafenib was cancelled after three weeks due to tumor progression and hemiplegia following brain metastasis and stroke. Periodical screening of the patient for oral findings allowed the non-mutilating excision of further oral metastases at an early stage with no signs of local recurrence during the follow-up period. Oral metastases from hepatocellular carcinoma appear to occur more frequently than formerly supposed.

Distant metastases of cancer to the oral region are rare (1). These lesions are usually found in terminal stages of cancer (1). Reports on liver cancer metastatic to the oral region are usually presented as single cases or small series and are compared with other reports presented in the literature (2-10). Few reports comprise oral metastasis from the liver in comparative studies on the subject of distant metastasis to the oral region (11). Treatment options are limited in these patients and oriented at pain relief and maintaining oral functions. Distant metastases to the oral region are predominantly from breast, lung and kidney cancer (11), and studies of this kind rarely differentiate between metastases settling in the oral soft tissues or bones. Distant metastases from liver carcinomas are very rare in studies from Western countries. In the study of Clausen and Paulsen (11), 1 out of 97 patients with oral metastases showed a histologically proven origin from liver carcinoma. This low percentage of liver metastasis to the oral cavity in relation to the overall number of metastases to the oral cavity and adjacent structures was confirmed in recent studies (12-14). However, a recent study from China on the sources of distant metastases to the oral region specifies liver carcinoma among the first five prevalent entities (15). The aim of this report is to describe the diagnosis, the course of the disease and the palliative treatment options in a patient who developed oral metastases from hepatocellular carcinoma. The first oral metastasis was the first finding of disseminated tumor spread.

Case Report

The 72-year-old male patient had been treated for a moderately differentiated hepatocellular carcinoma of pseudoglandular type by partial hepatectomy 5 months before admittance (tumor diameter: 16 cm; pT2, pNx, pMx, G2, V1, R0). Four months after hepatectomy, computed tomography (CT) of the trunk showed no tumor. On admission, the patient reported localized swelling of his upper jaw, extending into the oral cavity that had developed rapidly within 2 weeks after the CT scan. Oral investigation revealed an exophytically growing tumorous mass with localized disruption of the mucosal integrity (Figure 1A). With respect to the recent history of liver cancer the finding was suspected to be a distant metastasis of the primary.

The tumor was resected and showed no invasion of the zygomaticomaxillary complex. The excisional biopsy specimen was immediately fixed in formalin and sent to the laboratory. The tissues were paraffin embedded and routinely stained with hematoxylin-eosin, periodic acid Schiff (PAS) and Prussian blue. Immunohistochemistry was performed using avidin-biotin complex technique and diaminobenzidine as chromogen. The antibodies used included cytokeratin AE1/AE3 (M3515, dilution: 1:50; Dako, Hamburg, Germany) and HepPar1 (M7158, dilution: 1:50; Dako). We also performed appropriate routine positive and negative controls.
The oral mucosa was ulcerated (Figure 1C) and densely infiltrated by epithelial tumor with focal trabecular (Figure 1D) and pseudoacinar (Figure 1E) growth patterns. The cell plates were two to three cells thick. The tumor consisted of cuboid cells with rounded nucleus and prominent nucleolus next to optically clear cytoplasmatic vacuoles. Gland-like structures often contained bile. The immunohistochemical evaluation revealed a strong cytoplasmatic AE1/AE3 positivity and moderate to strong fine granular positivity of HepPar1 in the cytoplasm of tumor cells (Figure 1F). Our diagnosis was metastasis of hepatocellular carcinoma in soft and bone oral tissues pM1 (OSS).

We used positron-emission tomography for staging that revealed multiple areas of intense tracer uptake suspected to represent further metastases (lungs, adrenal gland, long bones). Therapy of multi-tyrosine kinase inhibitor (sorafenib, 2x200 mg/d) in due consideration of the multiplicity and distribution of metastases not allowing curative surgery was given. The chemotherapy was applied for 3 weeks and was interrupted after the patient sustained a cerebral infarction from extensive brain metastasis, becoming hemiplegic. During chemotherapy a single dose of zoledronic acid (4 mg, i.v.) was administered after diagnosis of multiple rib metastases that were causing pain.

During the follow-up, local oral tumor growth at the site of the first metastasis resulted in repeated oral bleeding that were successfully stopped by cauterization and three further debulking procedures during the next 5 months. Four months after first consultation, the patient developed two further oral metastases, one at the lingual side of the left mandibular alveolar process (Figure 1B) and a second at the hard palate. These small tumors were excised and did not grow again during the follow-up period. Healing of all oral sites was uneventful despite single intravenous application of a bisphosphonate. On the other hand, the tumor of the first metastasis extended to grow to the temporal fossa and terminally showed large skull osteolysis. Two months before death, a pathological fracture of the left humerus was stabilized with an intramedullary nail.

Thirteen months after the first therapy for liver cancer, the patient died with evidence of rapidly growing metastatic cancer. During this whole period, oral functions (speaking, chewing and swallowing) were maintained.

**Discussion**

Distant metastases to the oral cavity are usually a sign of poor prognosis (1). Metastasis from hepatocellular carcinoma is extremely rarely found in the oral and maxillofacial (OMF) region in western countries (1). However, a recent report on distant metastases to the oral region from China revealed primaries of the liver among the five most frequent entities with this type of spread. These authors stressed the hypothesis that ethnicity might interfere with the settling of oral metastases (15). Indeed, these authors compared prevalence data of oral and maxillofacial metastasis in the United States of America and China. They identified differences in the prevalence in ratios of primary cancer between both countries that were generally consistent with
the differences in their corresponding prevalent proportions in all malignancies. However, further analysis excluded a linear relationship between the constituent ratios in the oral and maxillofacial metastases and their prevalent proportions in all malignancies. There appears to be a different potentiality to form OMF metastasis in different types of cancer. In the case of cancer of the liver, the constituent ratios in OMF metastases were by far higher than the corresponding prevalent proportions in all malignancies. Therefore, in the case of an occult primary, cancer of the liver should also be suspected and emphasized in screening protocols (15). However, this excellent meta-analysis did not differentiate between osseous and soft tissue metastasis in the case of liver cancer.

Diagnosis of distant metastasis from hepatocellular carcinoma is based on a thorough elicitation of the patient’s history and allocation of adequate specimens for histological diagnosis. Conventional histology enables correct diagnosis of hepatocellular carcinoma in most cases. Further specification of the tissue by means of immuno-histochemical techniques might be anticipated in clinical studies designed to define chemotherapeutical targets (16, 17). Treatment for patients with distant metastasis to the oral cavity should be tailored to the individual situation. Maintenance of oral functions is a valuable therapeutic goal in palliative treatment.

There is apparently no difference concerning the prognosis between cases with oral metastasis as the first finding leading to diagnosis of the primary cancer and those patients who experience oral metastasis after therapy for hepatocellular carcinoma, with the date of oral findings as the reference time point. The mortality to incidence ratio was calculated as >0.8 (15).

Debulking of the oral tumor was effective in preserving the patient’s oral function up to the end of his life. We abstained from partial resection of the maxilla and cheek that would be a curative intention in the treatment of many malignant tumors arising in this area due to widespread metastatic tumor growth. Aggressive surgical treatment constitutes an option after solitary metastasis of hepatocellular carcinoma to the maxilla developing after liver transplantation as a curative therapy of the primary (18).

Oral bleeding occurred repeatedly during the follow-up period. In a current large survey on distant metastasis to the oral region, oral bleeding caused by a distant metastasis was noted in 14% (15). Frequent oral bleeding from metastases of hepatocellular carcinoma is at least in part attributable to the dense vascularization of the liver that is incompletely repeated in tumor tissues (18, 19). Embolization of the metastatic region was not required in the follow-up of this patient but is a valuable tool in other body regions and in some cases with osseous metastases, e.g. in the facial skeleton (20, 21).

Multiple oral metastases from hepatocellular carcinoma appear to be even more rare than solitary oral lesions. It seems noteworthy to refer to the time that elapsed from the resection of further oral metastases to the patient’s death, i.e. 4 months. Resection of these tumors was useful to avoid a mechanical obstruction of oral functions and a source of further oral bleedings.

Conclusion

We report on a patient with multiple distant metastases from hepatocellular carcinoma who maintained oral functions until the end of his life by means of resection and debulking of oral tumors. We advocate a palliative treatment concept for oral metastases aimed at alleviating the patient’s condition at a critical stage of their life.

References


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