Abstract. This report describes the diagnosis and treatment of a metastasis of a gastrointestinal stromal tumour (GIST) to the oral cavity in a 64-year-old female, 14 years after treatment for a gastric primary and 11 years after partial hepatectomy for regional recurrence. The metastasis grew slowly in the buccal soft tissues and became symptomatic by intraoral extension. Positron-emission tomography combined with computed tomography depicted a solitary space-occupying lesion in the right buccal region with high standardized uptake values. Surgical exploration revealed a ball-shaped firm tumour mass adhering to the adjacent tissues that was completely resected. Subsequent healing was uneventful. Six months following ablative surgery the patient was in good general condition. There were neither signs of local tumour recurrence nor further distant spread. However, the patient is now under continuous medication with imatinib. GIST metastases to the head and neck region are very rare. Two recent case reports about head and neck metastases of GIST showed a predilection for bone. This metastasis was solely located in the oral soft tissues.

Gastrointestinal stromal tumour (GIST) is a rare disease. The crude incidence rates of this soft tissue sarcoma are calculated 1.5 individuals per 100,000 persons and year (1, 2). Mean age at diagnosis is 58 years (range 16–94 years). GIST show a slight predilection for men (59%) compared to women (41%). GIST is localized in the stomach (50%), small intestine (25 %), colon (6%), rectum (9%), esophagus (2%) or omentum/mesenterium (5%). In about every second patient with first diagnosis of GIST further tumours are found simultaneously (3, 4). Metastases are located intra-abdominally in more than 90%. Less frequently affected at the time of first diagnosis are the bones (6%), lungs (2%) and other regions (2%) by GIST metastases (1). The standard treatment for GIST is surgery (1).

Metastasis of GIST to the head and neck region is very rare. Recently, Gil-Arnaiz et al. (5) reported on a tumour of the skull that proved to be a distant metastasis occurring simultaneously with the diagnosis of the primary GIST of the pelvic region. This tumour showed osteolytic properties of the calvaria on computed tomograms (CT). Imatinib was administered and the multiple lesions showed a partial remission for about 13 months.

Another recent report detailed the mandibular metastasis of a GIST (6). This patient was also treated with imatinib and survived 11 months after diagnosis. Both reports detail the diagnosis and treatment modalities in patients with osseous filiae of the craniofacial skeleton and both emphasize GIST metastases to the head and neck as being very rare events. This report adds the rare finding of a late metastasis to the oral soft tissues to the literature on GIST.

Case Report

History. A 64 year-old woman presented with an oral tumour in the right retromolar region. She had noticed a painless oral swelling for several weeks. On admission, the tumour was localized in the dorsal part of the cheek, protruded into the oral cavity and had started to interfere with the dental occlusion. During oral palpation, the tumour was firm and the covering oral mucosa was adherent to the underlying layers. Bimanual palpation proved the tumour to be immobilized in the soft tissues of the cheek (Figure 1). The covering buccal mucosa was completely unaltered and the patient had never noticed any laceration of this region. She had not paid attention to this finding until the occasion of a recent medical check-up for her abdominal tumour with the incidental finding of tumour depicted on a combined imaging. On positron-emission tomograms (PET) combined with a computed tomogram of the head and neck, a tumour of round shape was delineated in the right buccal region,
extending 2.3 cm maximum in diameter and was sharply demarcated by a high standardized uptake value (Figure 2). No other body region was suspected to bear a further tumour.

Approximately fourteen years ago, at the age of 51 years, a gastric tumour had been diagnosed and a partial gastrectomy was performed. Histological diagnosis at that time had revealed a low-grade leiomyosarcoma. Follow-up examinations were non-suspicious, including a hepatic lesion that was diagnosed in the following years and suspected to be a haemangioma. Three years after the first therapy, this hepatic tumour had become larger and was estimated to be a metastasis of the gastric cancer. A partial hepatectomy was performed at the age of 54 years. Histological diagnosis revealed a GIST. Taking account of the medical history of the patient, the specimens of the first operation were re-evaluated and substantiated the diagnosis of a metastatic GIST, arising from gastric primary.

After these two reportable events the patient had lived an event-free life for ten years and had never taken any medication to prevent tumour recurrence. Six months before presentation in our outpatient clinic an intra-abdominal recurrence was suspected, but not proven on ultrasonograms. To complete a thorough investigation, a PET/CT was performed that disclosed a solitary spot in the right buccal region (Figure 2).

**Treatment.** The tentative diagnosis was a distant metastasis of GIST to the oral cavity in due consideration of the medical history of the patient. The patient was subjected to ablative surgery via an intra-oral approach. The tumour was excised with adjacent soft tissues. Intraoperatively, the tumour was adherent to the surroundings and a partial excision of the masseter muscle was inevitable. Healing was uneventful by secondary intention. The patient was submitted to the Oncology Department. Chemotherapy with imatinib (STI571, Glivec®/Gleevec®, Novartis Pharmaceuticals, Basle, Switzerland) was scheduled (400 mg once a day). Six months after surgical therapy the patient’s general condition is good and no further metastasis has occurred.

**Histology.** Immediately after the excision biopsy of the buccal tumour, the tissue was fixed in 4% buffered formalin. The tumour was standard sampled, embedded in paraffin and stained with haematoxylin-eosin. The microscopic analysis revealed mesenchymal neoplasm containing spindle cells with moderate atypia (Figure 3A) and slightly
increased mitotic activity (up to 3 mitotic figures per 10 high power fields (0.16 mm²)). Necrosis of tumour tissue was not present. Immunohistochemical analysis (Table I) showed moderate positivity for vimentin (not shown) and CD117 (Figure 3B) along with strong reaction for CD34 (Figure 3C) and discovered on gist-1 (DOG-1), (Figure 3D). The proliferative activity detected using Ki-67 antibody (Figure 3E) was focally as high as 15%. Other immunohistochemical reactions (S-100, α-smooth muscle actin, desmin, β-catenin) showed negative results (not shown). Subsequent detection of CD117 (c-KIT, exon 9, 11 and 13) and platelet derived growth factor receptor alpha (PDGFRA, exon 12 and 18) mutations was performed. The sequencing analysis revealed a W557_V559>F mutation involving c-KIT exon 11.

Discussion

GISTs are the most common mesenchymal tumours of the gastrointestinal tract defined by expression of c-KIT (CD 117) (7-9). It is generally accepted that GISTs are derived from Cajal cells of the intestine. These cells appear to act as pacemakers of tract motility (10). However, the histogenesis, the diagnostic criteria and the evaluation of tumour behaviour have been the topic of controversial debate (9). This report describes the diagnosis and therapy of a GIST metastasis to the oral cavity. This metastasis occurred about 14 years after diagnosis of the primary, and 11 years after liver metastasis. Recurrence of GIST is typically intra-abdominal, with a predilection for liver metastasis (3). This was also diagnosed in our patient and had been successfully
cured by partial hepatectomy. Indeed, (late) recurrence of GIST appears to affect primarily the intra-abdominal organs, especially the liver (11, 12).

In several studies on GIST the rate and direction of distant spread was analysed (12, 13). The rate of extra-abdominal filiae ranged between 0 out of 96 patients (13) and 2% out of 200 patients (3). Current guidelines on soft tissue sarcomas estimate 50% of patients with GIST to have evidence of metastasis at the time of diagnosis, and argue in favour of a higher rate of metastases diagnosed outside the abdominal region: about 10% of metastases occur extra-abdominally (bone: 6%, lungs: 2%, others 1-2%, (1)). In a recently published analysis of distant metastases to the oral and maxillofacial region, numerous entities were registered, but no GIST (14). These data illustrate that distant metastasis of GIST to the oral and maxillofacial region is indeed a very rare finding.

Tumour size appears to be a dubious prognostic marker in GIST (15) and the anatomic distribution of this entity seems to be unrelated to patient outcome (2). DeMatteo et al. (3) also excluded the impact of location of the primary on survival. However, other reports showed that GIST arising in the stomach is less aggressive than GIST arising in the lower gastrointestinal tract (16). Woodall et al. (15) emphasize grade and metastasis as the most predictive parameters to determine survival of GIST patients.

This case is a stage IV cancer according to the UICC/AJCC classification of soft tissue sarcomas (17, 18). With regard to a proposal on a recent histopathological and prognostic tumour classification of GIST, patients with distant metastasis constitute a separate risk group. In these cases the size of the tumour and the mitotic index are irrelevant factors in estimating crude survival (19). This group has the lowest survival rate (18 months) and is distinct from the high-risk group (survival rate: 30 months) (1). Patients of the high-risk group have a lower crude rate than patients of the low-risk group (1). A current trinominal surgically orientated classification distinguishes between loco-regional spread and resectable tumour (R0), loco-regional spread and non-resectable
tumour, and metastatic disease with either resectable or non-resectable tumour (1). It is likely that some patients benefit from resecting recurrent tumour in cases with isolated local or metastatic disease, given the chance to resect this tumour completely (3). The high rate of local and distant tumour recurrence underlines the necessity for additional therapies (3).

Treatment with imatinib was introduced for patients with metastatic disease as an adjunct to surgery or in cases with non-resectable tumour. Imatinib proved to be effective in terms of overall survival and arrest of tumour progression (20, 21).

The c-KIT mutation identified in this case was recently published (22).

Conclusion

Distant metastases to the oral cavity are rare findings and are often an indicator of a late phase of a fatal disease. Some entities are more frequently encountered in this region than others, but GIST does not usually metastasize to the oral cavity. This report details the findings and treatment of a GIST metastatic to the buccal side of the oral cavity. Hopefully, the adjuvant chemotherapy is effective in dispelling the notion that the diagnosis of an oral metastasis is a signum mali ominis.

References


Table I. Immunohistochemistry (primary antibody, clone, source and dilution).

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