Neurofibromatosis type 1 (NF 1) is a syndrome with a predisposition for benign and malignant tumor development. Of the malignant neoplasms, osteogenic sarcomas are rare but have been described. There are some reports of patients with neurofibromatosis type 1 with a parathyroid adenoma and hyperparathyroidism. Also, there are studies that imply that the parathyroid hormone plays a role in the regulation and modulation of osteogenic sarcomas in vitro. We report about a 50-year-old female suffering from neurofibromatosis type 1, with a 3-year documented history of untreated hyperparathyroidism and a parathyroid adenoma. The patient developed a mandibular osteogenic sarcoma. To our knowledge, this is the first reported case occurring in the mandible. The unusual tumor site for a patient with neurofibromatosis type 1, the conjugation with hyperparathyroidism and the rapid growth of an osteogenic sarcoma are intriguing.

Keywords Neurofibromatosis type 1 · Hyperparathyroidism · Osteosarcoma

Introduction:

Osteosarcoma of the jaws is relatively rare and accounts for 6.5% of all sarcomas in the entire body. Nevertheless, it is the most common malignancy of the mandible [1, 5].

Case report

A 50-year-old female with NF 1 was referred to our outpatient clinic because of a swelling in her left parotid region. She first had noticed her swollen cheek several months earlier but asked for a medical consultation only after severe pain had begun. The patient had a documented history of hypercalcemia and hyperparathyroidism for 3 years prior to admission, but she had sought no medical attention nor received any treatment during that period. Her family history revealed that two of her children and two brothers suffered from NF 1. None of them had a malignant neoplasm.

A CT scan demonstrated a mass occupying the left parotid region, involving the ramus of the mandible and reaching into the infratemporal region.

The elevated blood calcium and parathyroid hormone, CT scan of the neck, ultrasound of the neck and Tc-99 MIBI scan were in accordance with the diagnosis of a parathyroid adenoma. CT scans of the chest, mediastinum and abdomen were normal.

A coarse-needle biopsy from the mass showed spindle and oval cells with few mitotic figures. Some multinucleated cells were also in the myxoid stroma. The cell stains were positive for vimentin, while negative for S-100 protein, keratin, and CD-45RA.

The patient underwent a total parotidectomy and partial mandibulectomy. The surgical findings were of a tumor with a size of $5 \times 4 \times 7$ cm, partially encapsulated and involving the mandible. It seemed to be adherent to its capsule but not to involve the
parotid gland. The superior border of the tumor involved the pterygoid muscles and infratemporal space.

The pathological findings (Fig. 1, Fig. 2) were of malignant spindle cells and giant cells with myxoid regions. The tumor cells showed numerous mitoses, many of them atypical. Prominent areas of malignant osteoid and bone formation with areas of necrosis were identified in the tumor mass. The tumor cells were strongly and diffusely positive for vimentin immunostain and focally positive for alpha-smooth-muscle actin and S-100 protein. Only a few of the tumor cells stained for keratin immunostain and were negative for myelin-basic protein, HMB-45 and CD-34. There was no involvement of the lymph nodes or the parotid salivary gland. Examination of the mandible revealed bone involvement. The diagnosis was of a malignant mesenchymal tumor with osteoid and bone formation consistent with osteosarcoma.

Following surgery, the patient received chemotherapy.

Discussion

Hyperparathyroidism and adenomas of the parathyroid in NF 1 patients are not common, but have been described [4, 10]. The suggestion that this condition might be associated with multiple endocrine neoplasia type 2 (MEN 2), neuroectodermal in origin, is interesting [4]. Our patient had an osteogenic sarcoma of the mandible, a mesenchymal-derived tumor in an unusual site for NF 1 patients. These tumors are not described in MEN 2.

The gene mutation responsible for NF 1 is transmitted in an autosomal-dominant fashion. This gene encodes for a cytoplasmic protein named neurofibromin, which is a negative regulator of Ras. Ras is a key protein in a major signal transduction pathway. Absence of neurofibromin increases the level of activated Ras-GTP, which leads to uncontrolled mitotic signals to the nucleus, and thus contributes to the proliferation of neurogenic sarcomas [3, 7].

PTH is a modulator of osteoblastic activity. This is by regulation of membrane-associated second messenger signal pathways. PTH is known to induce activity and growth in the ROS (rat osteosarcoma) 17/2.8 cell line [2, 6, 11]. Similar observations have been reported in human tissue; for example, Finkelman et al. found that PTH had a direct proliferative effect on TE-85 human osteosarcoma cells [8]. The results of these in-vitro studies suggest that PTH might play a role in the proliferation and growth of human osteogenic sarcoma cells in vivo.

Hyperparathyroidism associated with osteogenic sarcomas has rarely, if ever, been reported [9]. However, there is a recognized association between neurofibromata and hyperparathyroidism [4, 10]. The NF 1 patient we describe had a 3-year history of untreated hyperparathyroidism. In a fully documented latter period of several months, she developed a mandibular osteogenic sarcoma.

Although speculative, this could suggest that untreated hyperparathyroidism in NF 1 patients may lead to induction and growth of osteogenic sarcomas. This aspect of NF 1 requires further investigation.

References


Fig. 1 Osteoid formation (arrows) and presence of adjacent tumor cells with atypical nuclei and mitoses (HE ×400)

Fig. 2 Additional tumor region exhibiting dense sheets of tumor cells, few of them multinucleated with atypical nuclei and mitoses (HE ×400)