Clinical history
40 years old female with primary hyperparathyroidism. Fatty tissue of the left lower pole of the thyroid. Parathyroid tissue? Adenoma? Thymic remnants?

Macroscopy
Fresh tissue for frozen section 10 x 3 x 1.5 cm. Fatty tissue with induration of 3 x 2 x 1 cm (frozen section from this part). Macroscopically no parathyroid tissue detectable.

Microscopy
Fatty tissue with islands of hypercellular parathyroid tissue (approximate diameter 3 cm). No obvious capsule, no atypia, increased mitotic rate or vascular invasion.

Subsequent exploration of the left upper thyroid pole and the right side exhibited a small normocellular parathyroid gland in the lower right pole together with thymic remnants (not shown). No further parathyroid glands detectable.
Diagnosis
Left lower pole: Fatty tissue (3 cm diameter) containing islands of hypercellular parathyroid tissue consistent with a benign lipoadenomatous (hamartomatous) parathyroid lesion (nonencapsulated parathyroid lipoadenoma).

Discussion
The main finding in this case is an increased parathyroid cell mass associated with abundant stromal fat in a patient with primary hyperparathyroidism. No other cause for the hyperparathyroidism was found in subsequent examinations and the patient is cured after exision of the lesion.
In theory there are two possible situations in which the above mentioned combination can be found:
   1. Lipoadenoma of the parathyroid
   2. Lipohyperplasia of parathyroid glands

Parathyroid lipoadenomas and lipohyperplasia are extremely rare, constituting far less than 1% of all causes of primary hyperparathyroidism.

Parathyroid lipoadenoma is defined as benign neoplasm characterized by the proliferation of parenchymal and stromal elements. They usually present as an enlarged, mostly encapsulated mass with soft, yellow-tan cross section and increased weight (mean weight 1553 mg)\(^1\). The stroma of lipoadenomas is characterized by the abundance of adipose tissue (at least 30%) often associated with areas of myxoid change\(^2\) and fibrosis. The parenchymal elements include chief cells and small numbers of oncocytic cells arranged in thin, branching, cord-like fashion\(^3\).

Less than 50 cases of lipoadenomas have been described in the English literature until today. These lesions have also been called “parathyroid adenolipoma”\(^4\) or “parathyroid hamartoma”\(^5-7\). The term “parathyroid lipoadenoma” was introduced by Abul-Hay in 1962\(^8\) and has replaced the afore mentioned older terms.

In contrast to “ordinary” parathyroid adenomas, which more frequently occur in women parathyroid lipoadenomas have a 1:1 man-to-women ratio. They have been found in patients aged 41 to 92 years old\(^9\). The tumors show no predilection for a particular side or for superior or inferior glands and they may also occur at ectopic locations (e.g. in the mediastinum)\(^1\).

The etiology of these rare lesions is unknown. Some may appear as hamartomas with adjacent thymic remnants. Interestingly, in the series of Seethala et al., most of the patients with parathyroid lipoadenomas or hyperplasia were overweight with a BMI in the obese category\(^1\). In general, radiation therapy of the head and neck region in childhood is associated with a higher risk for primary hyperparathyroidism with a latency of 30 years\(^10\).

A rare variant of lipoadenoma is the so called “parathyroid lipothymoadenoma” in which thymic elements are an integral part and incorporated in the lipoadenoma\(^1,11\). Cases in which some thymic remnants are found in the fatty tissue adjacent to the tumor, should not be considered as lipothymoadenoma.

In the case of parathyroid lipohyperplasia, several or all glands are enlarged, exhibit an increased weight and contain more than 30% of fatty tissue. As in lipoadenoma, the total parathyroid cell mass is increased leading to symptoms of primary
hyperparathyroidism. There are only few reports in the literature describing these lesions, which are difficult to diagnose clinically and morphologically.\(^1,12,13\)

**Preoperative imaging**

Parathyroid lipoadenomas and lipohyperplasia are difficult to detect on preoperative imaging. This is due to the atypical appearance and high fat content. Thus, the fatty stroma may lead to diffusion of signal nullifying attempts at localization.\(^14\) On ultrasonography for example parathyroid lipoadenomas appear hyperechoic contrasting with the usual hypoechoic appearance of parathyroid adenomas.\(^15\) Many cases of false-negative imaging for parathyroid adenomas by nuclear scans, computed tomography and ultrasonography have been reported.\(^16-18\) Newer methods such as 3D-SPECT with sestamibi (technetium-99m-methoxyisobutylisonitrile) appear to be more sensitive for the localization of parathyroid lipoadenomas, particularly in the setting of multinodular thyroid disease and ectopic location, with a reported success rate of 71%\(^1\).

**Frozen sections**

The differentiation of lipoadenoma from normal parathyroid tissue on intraoperative frozen section may be very difficult, since in adulthood normal parathyroid glands may contain up to 30% of fatty tissue. Lipoadenomas can easily be overlooked or misdiagnosed as “normocellular” parathyroid tissue. That is why size and weight of an excised parathyroid gland have also to be taken into consideration before making the diagnosis of a “normocellular” parathyroid. Lipoadenomas are usually enlarged (mean weight 1553 mg), often show a fine capsule and may exhibit a rim of compressed normocellular parenchyma. If examined, the other parathyroid glands appear normal in size and morphology. In the case of parathyroid lipohyperplasia, all glands are enlarged and contain a high amount of fatty tissue. Another very important feature to diagnose lipoadenoma in the setting of frozen sectioning is the intraoperative PTH measurement.\(^9\) A decrease in intraoperative PTH levels of at least 50% frome baseline 10 minutes after parathyroid excision is a reliable predictor of long-term cure after parathyroidectomy for primary hyperparathyroidism.\(^9\) Fat stains usually show depleted intracytoplasmatic lipid to varying degree as in “regular” parathyroid adenoma, however, we do not use this technique for frozen sections at our institution.

**Differential diagnosis**

In patients with persistent hypercalcemia in the setting of “normal” or slightly lipohyperplastic parathyroid glands the possibility of familial hypocalciuric hypercalcemia (FHH) must be considered. FHH is an autosomal dominant disease which is caused by inactivating mutations of the calcium sensing receptor. Clinically, this disease is characterized by slight hypercalcemia, mildly elevated PTH, and low 24-hour urinary calcium excretion. Since the underlying etiology is not a parathyroid abnormality, surgical removal of parathyroid glands will not cure the patient\(^19,20\).

**References**