Pathologic Quiz Case

Recurrent Hypercalcemia

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45-year-old man with a history of hypercalcemia and cervical exploration at the age of 33 years presented with recurrent hypercalcemia (calcium level, 3.30 mmol/L; reference range, 2.10–2.65 mmol/L), elevated serum parathyroid hormone level (13.2 pmol/L; reference range, 1.0–6.8 pmol/L), perioral tingling, and a 12-lb weight loss. Exploratory surgery revealed a nodular mass measuring 2.5 × 0.6 × 0.5 cm and weighing 0.8 g at the site of prior surgery. Microscopic examination of the mass revealed nodules and cords of closely packed pleomorphic cells, with large, atypical nuclei infiltrating skeletal muscle (Figure 1). The nuclei had vesicular chromatin with occasional prominent nucleoli and mitotic activity (Figure 2). Immunohistochemical staining with MiB-1 revealed a tumor proliferation fraction of 7.0% (Figure 3).

What is your diagnosis?
Pathologic Diagnosis: Parathyroid carcinoma

Comment

The pathologic diagnosis at the time of the patient's first surgery was parathyroid adenoma. The elevated serum parathyroid hormone level originated from the parathyroid neoplasm rather than an ectopic source. Immunohistochemical staining of the current tumor is strongly positive for parathyroid hormone (Figure 4).

Distinguishing a parathyroid adenoma from a parathyroid carcinoma at the time of initial surgery can be diagnostically challenging in the absence of frank invasion or metastasis. In a study performed by Sandelin et al,16 of 40 cases of recurrent parathyroid carcinomas had been diagnosed as adenomas at the first operation. Our patient's history of a parathyroid adenoma at his original surgery illustrates this point. Li Volsi et al2 attribute the difficulty of diagnosing parathyroid carcinomas to their rare incidence (only 1%–2% of cases of primary hyperparathyroidism) and a paucity of specific histologic criteria. In a study of 50 cases of parathyroid carcinoma, diagnosed on the basis of extraglandular invasiveness or tumor recurrence, Bondeson et al3 found no mitotic figures in 11 cases and no nuclear atypia in 7 of 21 metastasizing tumors. Pleomorphism is not uncommonly found in parathyroid adenomas, and cytologically bizarre focal areas may be seen in 10% of cases.4 In addition, pyknotic nuclei, which may resemble mitotic figures, are present in adenomas.4

The need for objective criteria to assist in the differential diagnosis of parathyroid adenomas and carcinomas has led to recent studies of the cell cycle–associated antigen Ki-67, which is expressed in all cells that are not in the G0 phase of the cell cycle.5–7 In these studies, Ki-67 immunostaining with MiB-1 antibody was found to be useful in distinguishing parathyroid adenomas from carcinomas and revealed statistically higher mean tumor proliferation fractions (TPFs) in carcinomas. In a study by Lloyd et al8 of 24 parathyroid carcinomas and 35 adenomas, the mean TPF was 7.1% ± 1% in the carcinomas vs 2.4% ± 0.2% in the adenomas. Since none of the adenomas had TPFs greater than 5.3%, it was concluded that a parathyroid neoplasm with a TPF greater than 6% is likely to be a carcinoma.5 Abbona et al6 similarly concluded that a TPF greater than 6% is consistent with the diagnosis of parathyroid carcinoma. Vargas et al7 also found a significantly higher mean TPF in carcinomas than adenomas (8% vs 2%, respectively). Since only 1 of 10 adenomas had a mean TPF greater than 4% and only 2 of 11 carcinomas had a mean TPF less than 4%, the authors concluded that a TPF greater than 4% supported a diagnosis of malignant neoplasm.2 Immunostaining with MiB-1 in our case revealed a TPF of 7.0%, which was consistent with these findings in supporting the diagnosis of carcinoma.

The prolonged interval between the first and second surgical procedures (12 years) in our case demonstrates the slow growth of many parathyroid carcinomas.4 In the study by Sandelin et al,1 9 of 40 patients with recurrent parathyroid carcinoma were alive at follow-up 9 to 25 years after the first surgery. Death is usually caused by hypercalcemia rather than local tumor invasion or tumor metastasis.8

References