P-5

Functional Neuroendocrine Neoplasms (NENs) With Parathyroid Hormone–Related Peptide (PTHrP)-Mediated Hypercalcemia: A Retrospective Study

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BACKGROUND

PTHrP-mediated hypercalcemia in NENs is extremely rare, with only a few reported cases. This study aimed to characterize its clinical features, management, and outcomes.

METHODS

This retrospective multicenter study included adults with confirmed NENs and documented PTHrP-mediated hypercalcemia across three Mayo Clinic sites. Clinical, laboratory, and treatment data were extracted from the electronic medical record. Outcomes included calcium normalization, recurrence patterns, and treatment response. Data were analyzed descriptively.

RESULTS

A total of 15 patients with NENs and PTHrP-mediated hypercalcemia were identified. Median age at hypercalcemia onset was 62 years (interquartile range [IQR], 57.5–67.5), and 11 (73%) were male. All tumors were pancreatic in origin and well differentiated, with a median Ki-67 index of 8% (IQR, 5–12.6). Hypercalcemia was present at NEN diagnosis in 11 (73%) and developed later during disease progression in 4 (27%). At hypercalcemia onset, 13 (87%) had metastatic disease, all with liver involvement, while 2 (13%) had locally advanced disease. Supportive management included hydration plus bisphosphonates in 12 (80%) and denosumab in 1 (7%). Among 13 patients receiving supportive therapy, normocalcemia was achieved with supportive therapy alone in 2 (15%), and only after the addition of subsequent cancer-directed therapy in 9 (69%) patients. Among 2 nonresponders (15%), 1 normalized after switching to denosumab and 1 remained hypercalcemic despite multiple supportive and cancer-directed therapies in the setting of continued disease progression. Cancer-directed treatment to achieve normocalcemia was used in 13 (87%) patients, which included systemic treatment (CAPTEM, SSAs, PRRT, everolimus, temozolomide) in 10 (77%) patients and locoregional therapy in 3 (23%), all of whom underwent surgery. Overall, hypercalcemia recurred in 6 of 14 patients who achieved normocalcemia (43%), with a median time to recurrence of 8.1 months.

Recurrence coincided with radiographic progression in 4 (67%), while 2 (33%) recurred without radiographic progression. Among patients with recurrence, 1 responded again to bisphosphonate therapy, while the remaining 5 patients were refractory to further supportive and cancer-directed therapies. Notably, among the 3 patients who underwent debulking surgery, calcium normalized immediately after surgery and did not recur.

CONCLUSIONS

Supportive therapy alone achieved normocalcemia in a minority of patients with PTHrP-secreting pNETs. Most patients required cancer-directed therapy, and recurrent hypercalcemia was frequently refractory to additional treatment. Surgical cytoreduction was associated with rapid and durable calcium control in selected patients.

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