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The Clinical Course of Duodenal Ulcer Associated with Hyperparathyroidism

Melvin A. Block, M.D.*; Boy Frame, M.D.**; and Thomas A. Fox, Jr., M.D.***

In 98 patients with primary hyperparathyroidism, 15 had objective evidence of duodenal ulcer disease. Following operative correction of the hyperparathyroidism, improvement of duodenal ulcer disease occurred usually, but not uniformly, if unassociated with non-beta islet cell tumors. Correction of hyperparathyroidism in patients with the Zollinger-Ellison syndrome does not significantly influence the peptic ulcer which should be given primary aggressive surgical treatment.

Although the association is not frequent, there appears to be an increased incidence of duodenal ulcer disease in patients having primary hyperparathyroidism. A natural question is the influence of correction of the hyperparathyroidism and its associated hypercalcemia on the course of demonstrated duodenal ulcer disease. It led to this review of our experience.

Clinical Experience

Through 1969, of 98 patients for whom the diagnosis of primary hyperparathyroidism had been confirmed, 15 also had evidence of duodenal ulcer disease demonstrated by radiologic study, operation, or autopsy. Patients with primary hyperparathyroidism frequently complain of digestive tract symptoms which may be compatible with duodenal ulcer disease and which may disappear after surgical correction of the hyperparathyroidism. However, unless the presence of a duodenal ulcer was confirmed by x-ray such patients were omitted from this study. Also omitted was one patient with laboratory evidence of hyperparathyroidism at the time of operative treatment for duodenal ulcer because surgical exploration of the parathyroids, to confirm the diagnosis of hyperparathyroidism, was not performed.

The clinical course of the 15 patients with the association of duodenal ulcer disease and primary hyperparathyroidism is outlined in Table I. Of the total group, 8 were females and 7 males, 3 of the females having, in addition, non-beta islet cell tumors of the pancreas.

As is evident from Table I, the clinical course necessitated separation of patients with duodenal ulcer disease and hyperparathyroidism into two ma-
| Status of Activity of Duodenal Ulcer | No. Pts. | Age of Pts. | Course After Surgical Correction of Hyperparathyroidism | | | | | | | | Ulcer Improved | Recurrence | Recurrence Required Operation | Duration Follow-up in Years | Died of Ulcer Prior to Operation on Parathy. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not associated with islet cell tumors of pancreas | | | | | | | | | | | | | | | |
| Ulcer active at time of operative correction of hyperparathyroidism | 8 | 38-68 | 44 | 7 | 1 | 1 | 1-11 | 6 | - |
| Ulcer inactive at time of operative correction of hyperparathyroidism | 3 | 49-69 | 60 | - | 0 | 0 | 1-5 | 3 | - |
| Ulcer operation required prior to recognition of hyperparathyroidism | 1 | - | 69 | - | 1 | 0 | - | - | - |
| Associated with non-beta islet cell tumor of pancreas (ulcer active) | 3 | 39-53 | 46 | - | - | 1 | - | - | 2 |
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Major groups on the basis of the presence or absence of islet cell tumors producing manifestations of the Zollinger-Ellison syndrome. Although the total number of patients involved does not permit a valid statistical analysis, the virulence of the duodenal ulcer disease associated with non-beta islet cell tumors is obvious in this experience, and conforms with recognized characteristics of the Zollinger-Ellison syndrome. Even though in one such patient the associated hyperparathyroidism was corrected first, severe duodenal ulcer disease continued until total gastrectomy was accomplished. Two other patients succumbed from complications related to perforation of peptic ulcers before surgical consideration could be given to associated hyperparathyroidism.

Duodenal ulcer disease unassociated with the Zollinger-Ellison syndrome was less severe and usually improved symptomatically following surgical correction of primary hyperparathyroidism. However, one of eight patients in whom the ulcer appeared to be active at the time of the parathyroid operation required surgical correction four years later for a recurrent symptomatic, bleeding duodenal ulcer. There was no evidence of recurrent hyperparathyroidism in this patient. Although active ulcer disease had been present previously in three patients, the ulcer was clinically quiescent at the time of removal of a parathyroid tumor. One other patient had undergone operative correction of a duodenal ulcer and had no further difficulty with peptic ulcer disease for the 13 years prior to removal of a parathyroid tumor and for the subsequent nine years.

A single parathyroid tumor was found in all of the patients with duodenal ulcer disease unassociated with islet cell tumors. Abnormalities in multiple parathyroid glands were present in the three patients with the Zollinger-Ellison syndrome.

Discussion

This study conforms with previous reports indicating a small increase in the incidence of duodenal ulcer disease in patients with primary hyperparathyroidism. However, our experience emphasizes the clinical necessity of separating patients having concomitant duodenal ulcer disease and primary hyperparathyroidism into two groups on the basis of the presence or absence of non-beta islet cell tumors.

For patients not demonstrating features of the Zollinger-Ellison syndrome, our experience, although not statistically firm, corroborates that of others in indicating that correction of primary hyperparathyroidism usually results in the amelioration of duodenal ulcer disease. However, the overall experience suggests that duodenal ulcer disease in patients with primary hyperparathyroidism unassociated with islet cell tumors is not particularly aggressive and probably runs a course not greatly dissimilar from that unassociated with hyperparathyroidism.

Correction of hyperparathyroidism does not guarantee freedom from serious difficulty from a duodenal ulcer. This was shown by one patient who later required operation for further complications from his ulcer. Furthermore, in three patients a previously ac-
tive duodenal ulcer was inactive at the time of the parathyroid operation. Variations occur in the severity of duodenal ulcer disease in patients with hyperparathyroidism. Not all patients having primary hyperparathyroidism demonstrate excessive gastric secretion. The hypercalcemia and other effects of primary hyperparathyroidism, although aggravating factors, are probably not major determinants in the etiology of duodenal ulcer disease in these patients.

Correction of hypercalcemia does not appear to significantly alter the course of duodenal ulcer disease in patients with non-beta islet cell tumors of the pancreas. Although hypercalcemia conceivably exaggerates duodenal ulcer disease in these patients, other factors are more important in producing the extreme virulence of the ulcer in the Zollinger-Ellison syndrome. Hyperparathyroidism should be given secondary consideration in such patients since aggressive surgical control by total gastrectomy as early as possible is indicated. Aggravation of duodenal ulcer disease by other endocrine lesions was not evident in this study.

Experimental studies support the view that hypercalcemia influences gastric secretion, although it is probably not a critical factor. Species differences make animal studies of questionable significance for man. Evidence indicates that in man hypercalcemia results in an increased basal secretion of hydrochloric acid as well as an increase in the volume of gastric juice, a decrease in pepsin secretion, and an increase in mucous secretion. These changes do not appear to be the result of direct effects of parathyroid hormone since administration of this agent has no predictable influence on gastric secretion. Hypercalcemia in man produces elevated blood levels of gastrin, particularly in patients with duodenal ulcers, and this then is the likely cause of calcium-induced increased gastric acid secretion. It appears that the influence of hypercalcemia on the secretion of gastric acid is mediated in some manner through the vagus nerve. There does appear to be a direct relationship between the level of serum calcium and gastric secretion. These effects of hypercalcemia, however, are based on acute or short-term studies, so that long term results in patients with hypercalcemia are not conclusive. Nevertheless, basal gastric secretory studies show a reduction following operative correction of primary hyperparathyroidism.

Duodenal ulcer disease, unassociated with endocrine disease other than hyperparathyroidism, usually does not appear particularly serious. But, if severe, it does require therapy on the basis of usual indications. The behavior of ulcer disease associated with hyperparathyroidism may follow one of three general patterns:

1. Heals spontaneously, or after gastric operation, with persistent hyperparathyroidism.
2. Persists with temporary remissions but heals after correction of hyperparathyroidism.
3. Persists or recurs after operative correction of hyperparathyroidism; in such patients the coexistence of the Zollinger-Ellison syndrome should be considered.
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Summary and Conclusions
1. Of 98 patients with primary hyperparathyroidism, the clinical course of an associated duodenal ulcer present in 15 depended primarily on the presence or absence of co-existent non-beta islet cell tumors of the pancreas.

2. Although hypercalcemia may exaggerate the virulence of duodenal ulcer disease in patients with the Zollinger-Ellison syndrome, correction of hypercalcemia does not significantly improve the duodenal ulcer. Operative treatment, consisting of a total gastrectomy in nearly all instances, should be urgently provided for such patients prior to operative consideration for the hyperparathyroidism.

3. Although active duodenal ulcer disease in the absence of the Zollinger-Ellison syndrome usually improves following operative correction of associated primary hyperparathyroidism, this is not uniformly true. Hypercalcemia appears to be only one factor, and not always a dominant etiologic factor in the duodenal ulcer disease which varies in severity in these patients.

4. In patients with active duodenal ulcer disease associated with primary hyperparathyroidism in the absence of the Zollinger-Ellison syndrome, the ulcer should be treated on the basis of its own merits with consideration given to correction first of the hyperparathyroidism if usual surgical indications for the ulcer do not exist.

REFERENCES
Block, Frame and Fox


