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CASE REPORT

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Burnett and his co-workers[1] in 1949 described a syndrome which occurred in patients consuming excessive amounts of milk and absorbable alkalies for symptoms of peptic ulcer. In addition, Burnett's series of six male patients presented other interesting features which included, hypercalcemia without hypercalcuria or hypophosphatemia, normal serum alkaline phosphatase levels, marked renal insufficiency with azotemia, mild alkalosis, calcinosis including an ocular lesion, and improvement following a restriction in dietary calcium and the elimination of alkali therapy. Burnett recognized that primary hyperparathyroidism could not be excluded with certainty in all patients. This difficult differential diagnosis has been recognized in several later reports[2,3,4,5]. The following history presents such a problem of differential diagnosis in a patient with chronic duodenal ulcer and bilateral nephrolithiasis.

CASE REPORT

L. P. No. 417503, a 59-year-old male was first seen at Henry Ford Hospital in 1947 when he was 49 years of age. His chief complaint was gross hematuria. He was found to have bilateral ureteral calculi and right renal calculi. The left kidney function was diminished in the intravenous pyelogram study. However the voided urine was concentrated to a specific gravity of 1.021. The blood hemoglobin was 14.6 gm. His past history included a chronic duodenal ulcer which had bled twenty-five years previously. The ulcer had been self-treated with milk in quantities up to two quarts daily. Sodium bicarbonate had been consumed daily for many years and there were weeks when he had purchased two half-pound boxes of the antacid, representing an approximate daily dose of 65 grams.

In 1953, symptoms of polyuria, polydipsia, weakness and pain in the legs led to his hospitalization. Blood pressure was 190/100. There was slight pedal edema. A specific gravity of 1.006, traces of albumin and an occasional red blood cell were found in the urinalysis. The hemoglobin was 11.8 gm. and total serum bilirubin, 0.23 mg. Bromsulfalein retention and the liver flocculation tests were negative. The serum albumin was 4.3 and globulin 1.9 gm., while serum calcium was 11.8 and phosphorus 4.0 mg. Basic phosphatase was 1.42 Bodansky units. Serum sodium was 139, chlorides 79, potassium 4 and CO2 capacity 33.8 m.Eq per liter. The plasma non-protein nitrogen was elevated to 130 mg. percent. The standard urea clearance was 12 cc. and 11 cc. per minute. Urine culture grew a non-hemolytic streptococcus and Bacillus subtilis. The stool was negative for occult blood. An electrocardiogram was normal. Because of a deeply pigmented skin, Addison's disease was considered and the eosinopenic response to ACTH administration was determined. The drop in cell count from 172 to 125 was subnormal, but the studies pertaining to this diagnosis were not carried further.

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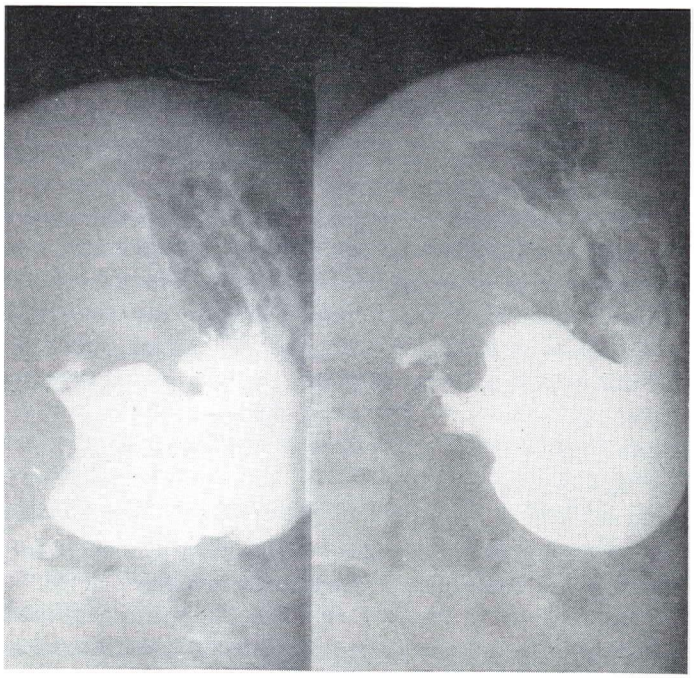

FIGURE 1 Obstructing duodenal ulcer deformity with retention of barium in the stomach.

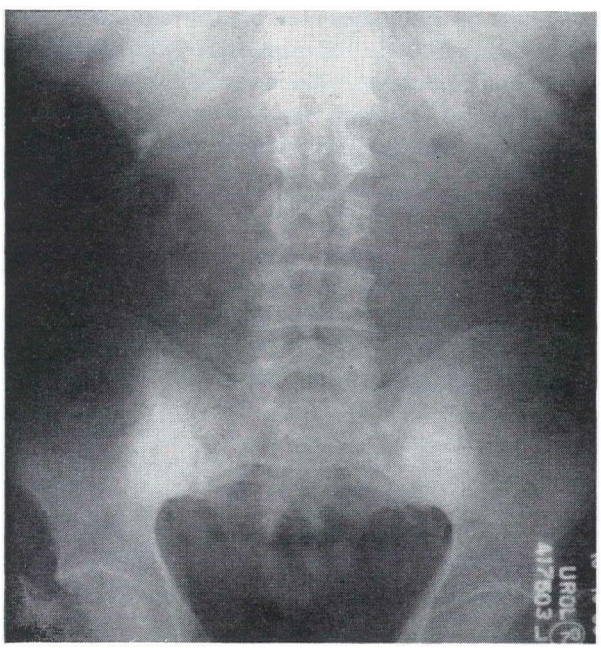

FIGURE 2 Bilateral nephrolithiasis and o dense osseous sclerosis of the sacroiliac joints.

The heart was found to have a hypertensive configuration by roentgen examination of the chest. X-ray studies of the skull and colon were normal. A deformed cap was seen in the x-ray of the duodenum and retention of barium in the stomach indicated an obstructing cicatrix (Fig. 1). Bilateral nephrolithiasis and an osseous sclerosis of both sacroiliac joints were seen in the roentgen film of the abdomen (Fig. 2).

A diagnosis of the milk-alkali syndrome was made, and the patient was cautioned to avoid soda bicarbonate. The blood pressure gradually returned to normal. One month later he was symptom-free and the NPN had reduced to a level of 24 mg. percent. Subepithelial deposits of calcium, concentric with the limbus, were found later by slit lamp examination of his cornea. During subsequent office visits a succussion splash was heard in the upper abdomen. The highest acidity was 88 degrees of free hydrochloric acid in a fractional gastric analysis. Various types of aluminum hydroxide gels were prescribed, but these were discarded by the patient. Preparations containing magnesium salts caused a burning distress in the epigastrium; while aluminum phosphate gel and preparations containing calcium were interdicted because of the renal dysfunction. Dihydroxy aluminum aminoacetate gel was tolerated fairly well.

The patient remained free from ulcer distress and symptoms of renal failure. However the hemoglobin dropped to 9 grams and hematocrit to 34. In early 1955 the non-protein nitrogen was 73 mg. percent. The 24-hour urinary calcium excretion was 185 mg., although the collection was not made while he was on a low calcium intake. A Sulkowitch test of the urine was not strongly positive. More detailed metabolic studies were requested of the patient, but he was unable to complete them.

In August, 1955, the patient ingested sodium chloride tablets during a week of travel in hot weather. His weight abruptly increased four pounds and he became dyspneic and orthopneic. Hypertension was again present, the blood pressure being 190/100. A specific gravity of 1.005, traces of albumin and 2-5 red blood cells per H.P.F. were found in the urinalysis. The blood hemoglobin was 9.9, serum albumin, 5.0 and globulin, 1.8 gm. The serum CO2 was 16.2 and chlorides, 104 m.Eq. per liter. Maximal urea clearance was 17 cc. per minute. A phenolsulfonphthalein excretion was 10 percent. The electrocardiogram was normal.

After a short period of sodium restriction, the patient was able to resume his activities without symptoms. During the following year his hemoglobin fell to 8.4 gm. and he again complained of fatigue. In August, 1956, he was transfused with 1000 cc. of whole blood after therapy with ferrous sulfate had failed to correct the anemia. Except for pruritis, he has continued free from symptoms. The skin has remained deeply pigmented and small pruritic papules on the back and shoulders have appeared on two occasions.

DISCUSSION

This patient has presented essentially all the clinical and metabolic features of the original description of the milk-alkali syndrome[1]. The history was well established that excessive milk and absorbable alkali were used over many years for symptoms of a chronic duodenal ulcer. It is significant that ocular band keratopathy was noted during slit-lamp study, since this was the only physical finding common to all of Burnett's six patients and to 16 of the 21 patients reviewed by Kessler[6]. Renal calculi

were present bilaterally and an ossifying sclerosis was observed in the x-rays of the sacro-iliac joints. There were no findings in the skeletal x-rays which suggested hyperparathyroidism.

Although there was impaired renal function when the patient was first seen, a definite metabolic alkalosis was indicated by a serum CO2 level of 33.8 m.Eq. per liter. As renal function was compromised further, and the absorbable alkali was withdrawn, the alkalosis was superceded by an acidosis of moderate severity. The renal insufficiency was demonstrated by the urea clearance tests and clinically on two occasions by the development of azotemia, hypertension and anasarca following the ingestion of excessive salt.

We lack clear evidence of antecedent renal impairment. However, if present it was not advanced, since extensive renal or ureteral calculi would not be expected to develop in a kidney with markedly curtailed excretory function. We believe the hypercalciuria and hyperphosphaturia of excessive milk ingestion was possible only with adequate renal function. Precipitation in urine containing such high mineral content would be facilitated greatly by the chronic alkalosis, just as in urine made alkaline by urea-splitting organisms. There is evidence that milk and absorbable alkali adversely affect kidney function[8], and that the damage from alkalosis may be aggravated by excessive calcium loads[2].

Other metabolic features included a moderate hypercalcemia and normal phosphatemia while the patient received a standard hospital diet. The Sulkowitch reaction and 24-hour urinary calcium excretion were not excessive for an unrestricted diet. The serum albumin concentration was increased, as noted originally by Burnett[1]. Failure to obtain further metabolic data resulted from the patient's unwillingness to re-enter the hospital for study.

The final feature of the similarity between our patient and those of Burnett's study is the clinical improvement after eliminating the absorbable alkali and excessive milk. A deeply pigmented skin and pruritic papules on his back and shoulders have been observed, similar to lesions reported by Burnett[1] and Kyle[2]. The azotemia, hypertension and edema have cleared without specific therapy other than sodium restriction. Permanent renal damage probably has resulted since there is a metabolic acidosis and a chronic hypochromic anemia which has been refractory to treatment. No occult bleeding from the duodenal ulcer has been found. The electrocardiographic abnormalities that may accompany this syndrome[7] were not present.

As emphasized by other authors, the differentiation of the milk-alkali syndrome from hyperparathyroidism may be difficult. Kyle[2] stated that an improvement on a diet low in calcium and absorbable alkali is the only differential feature. The observations of Chambers and associates[9] that the hypercalcemia of hyperparathyroidism may be accentuated by a restriction in dietary phosphorus suggests that such dietary restrictions may have diagnostic value. The finding of a metabolic alkalosis which clears when the patient restricts alkali ingestion does not decisively eliminate the diagnosis of hyperparathyroidism, since this treatment might be adopted by a patient with hyperparathyroidism who also has a peptic ulcer. The frequency of ulcer-like symptoms in patients with hyperparathyroidism has been recognized as a major confusing feature in the differential diagnosis.

The presence of calcinosis and band keratopathy of the eye are not strongly distinguishing features, but they tend to favor either the milk-alkali syndrome or vitamin D poisoning. Assuming the same degree of renal impairment in each, the patient with the milk-alkali syndrome likely would have extra-skeletal calcification earlier than the hyperparathyroid patient. Dworetzky[10] and Poppel et al[11] have observed improvement in patients with calcinosis when a low calcium diet was employed.

When clinical features and blood indices have suggested or strongly indicated a diagnosis of hyperparathyroidism, the finding of hypercalciuria has been the usual supportive or confirmatory index. With advanced renal failure in hyperparathyroidism however, urinary calcium may be low[3] and phosphate retention may mask a previously diagnostic hypophosphatemia[5]. In the presence of advanced renal insufficiency, surgical exploration of the parathyroids and critical histological study of the sections may be necessary to differentiate the two disorders. More recently the tolerance test of intravenous calcium[3] and the phosphate reabsorption test have been employed. The limited data regarding the use of such procedures in the study of patients with the milk-alkali syndrome suggest that they were of diagnostic value[3]. Also, renal insufficiency is likely to modify the tubular handling of phosphate and thus limit their diagnostic value.

We believe the evidence presented in the case report of our patient favors a diagnosis of the milk-alkali syndrome rather than a diagnosis of hyperparathyroidism. The two most helpful though not decisive observations have been the azotemia with alkalosis and the continuing improvement of the patient when he was given a diet low in calcium and absorbable alkali.

SUMMARY

A case report of the milk-alkali syndrome is presented to illustrate the metabolic abnormalities of this disease and its difficult differentiation from hyperparathyroidism.

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