Clinical spectrum of primary hyperparathyroidism

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ABSTRACT

Objectives: Primary hyperparathyroidism (1HPT) is now being diagnosed with increasing frequency. Simultaneously there has been an apparent change in the presentation of the disease and indications for surgery. The aim of this study was to examine the clinical presentation, indications for surgery, and outcomes of neck explorations for primary hyperparathyroidism.

Methods: This study was carried out over a 12 year period, January 1990 to April 2002 at Jordan University Hospital, Amman, Jordan. Information on the indications, procedure performed, pathology and complications of all neck explorations for 1HPT was obtained from a retrospective thyroid/parathyroid surgical database. A minimum of 12 months follow-up was required in order to determine outcome of surgery.

Results: Out of 40 patients diagnosed with primary hyperparathyroidism at Jordan University Hospital, Amman, over 12 years, 14 patients (35%) diagnosed 4 years after the onset of their disease. Severe bone disease was the main indication for surgery in 28 patients; 5 patients with fractured bones, 2 patients with bone cysts, 3 patients with brown tumors and severe osteoporosis and backache in 22 patients; renal calculi in 10 patients; muscle ache and weakness in 14 patients; acute pancreatitis in one patient and asymptomatic HPT following biochemical screening in one patient. Two patients continued to have persistent hypercalcemia after the first operation; one of them has been cured by reoperation for an ectopic parathyroid in the anterior mediastinum resulting in an overall cure rate of 97.5%.

Conclusion: This study showed that severe bone disease with fractures, bone cysts and brown tumors are still the most common presentation of primary hyperparathyroidism in Jordan; this is most likely due to delay in diagnosis and initiation of treatment. It is important to screen for hyperparathyroidism in high risk patients and to refer these patients to specialized centers for proper management.

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Once a common manifestation of hyperparathyroidism, the classical cystic bone disease, and renal calculi described by Albright et al[1] are seen only in a minority of patients and a new pattern of the disease has emerged characterized by a subtle and vague symptomatology.[2] Today patients with primary hyperparathyroidism (1HPT) present most commonly with mild elevation of serum calcium concentration along with increased parathyroid hormone levels or inappropriate "normal"parathyroid hormone levels to the settings of hypercalcemia.[2-4] Many such patients are described as "a symptomatic"however, if carefully questioned they often reveal symptoms such as tiredness, muscle weakness, constipation and depression, many of which resolve after surgery.[4,5] Screening for bone mineral density by osteodensitometry has added a further potential indication for parathyroid surgery and has become the most common indication for surgery in some

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centers.[6] Primary hyperparathyroidism in Jordan still a disabling disease presents with fractured bones, Brown tumors and neuromuscular weakness. This study was designed to examine the spectrum of presentation of 1HPT at Jordan University Hospital, indications for surgery and outcomes of parathyroidectomy.

Methods. From January 1990 to April 2002, 40 consecutive patients underwent neck exploration for a preoperative diagnosis of 1HPT, at Jordan University Hospital, Amman, Jordan. The diagnosis was based on the finding of elevated serum calcium concentration (>10.5 mg/dl), or inappropriately normal or elevated parathyroid hormone (PTH) levels (>54 pg/ml). We have examined the demographics, surgical indications, operative techniques and post operative complications, pathology, and immediate and long term disease status. Thirty-eight patients were followed for a minimum of 12 months and 2 patients had only 2 months follow-up as of recent surgery. Persistent 1HPT was defined as hypercalcemia that became an evident within 6 months of the operation. All patients have bilateral neck exploration in an attempt to visualize all parathyroid glands and frozen section biopsies were taken in some cases to confirm the presence of parathyroid tissue in small adenomas (<100 mg) as it might be difficult in these cases to differentiate between parathyroid tissue and lymphoid tissue. The diagnosis of parathyroid adenoma depends on the gross appearance of the remaining glands, the weight and the presence or a rim of normal parathyroid tissue in the removed gland which is difficult to document on frozen section analysis.

Results. There were 8 (20%) male and 32 (80%) female patients with an age range of 16-72 years. All the patients were followed for a minimum of 12 months after operation. The average preoperative serum calcium level was 10.68 ± 1.2 mg/dl, serum phosphorous 2.5 ± 1.5 mg/dl, the intact PTH level was 438.2 ± 398 pg/ml and the alkaline phosphatase 296.7 ± 245.9 IU/L. The diagnosis of 1HPT was established after 4 years from the onset of symptoms in 14 patients, after 3 years in 7 patients, after 2 years in 7 patients and in less than 2 years in 12 patients **(Table 1).** Four patients in this series were diagnosed initially to have bone metastasis of unknown origin or thought to have multiple myeloma which, could not be confirmed by specific investigation. Severe bone disease was the main indication for surgery in 28 patients; 8 had fracture bones, bone cysts in 2 patients, Brown tumors in 3 **(Figures 1a, 1b, 1c)** and severe osteoporosis and backache in 22 patients; renal calculi in 10 patients; muscle ache and weakness in 14 patients; pancreatitis in one patient and asymptomatic HPT following biochemical screening in one patient. The final pathology was single adenoma in 31 (77.5%), 2 adenomas in one (2.5%), hyperplasia in 8 (20%) and hypocalcemia requiring calcium supplementation immediately postoperatively was seen in 18 patients. Four patients remained hypocalcemic requiring long term calcium supplement, and 6 patients continued to receive calcium and Vitamin D supplement for severe osteoporosis. Hypercalcemia was cured immediately in 38 of the 40 patients with a success rate 95%. Two patients had persistent hyperparathyroidism; one patient had had mediastinal tumor required sternal splitting with calcium returning to normal post operatively, the other patient had a rheumatologic disorder (CREST syndrome) and she refused further intervention.

Discussion. Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients and is the 2nd most common cause of hypercalcemia (after malignancy) in hospitalized patients.[7] It occurs in 0.2-0.5% of the population.[5-7] It is more common in women than in men with a peak incidence between the 5th and 6th decades of life and a sharp rise in prevalence after the age of 50.[7-9] In this study we reviewed our experience with hyperparathyroidism in 40 cases diagnosed and treated at Jordan University Hospital, between 1990 and 2002. As demonstrated by our data, severe bone disease with fractured bones, bone cysts and brown tumors is still the most common form of presentation in Jordan. Most of our patients present late in the course of their disease after having the disease for many years with non specific symptoms attributed by the patient mainly to aging or failure of treating physicians to suspect hyperparathyroidism as a cause of their complaints. Osteitis fibrosa cystica, characterized by bone cysts, Brown tumors of the bones, subperiosteal resorption of the distal phalanges and clavicles although rare is still reported in some series.[10-12] Such osteolytic lesions are misdiagnosed as metastatic bone disease. This usually leads to futile investigations to locate a primary and above all to a severe psychological trauma for the patient and his family. Several investigations can help differentiate between these 2 entities as shown in **Table 2.** The pathology of bone disease in 1HPT involves excessive osteoclast resorption with destruction of cortical bone and creation of fibrous cysts.[11] Bone densitometry studies on cortical and cancellous bone show the 2 skeletal compartments to be differently affected in 1HPT with preferential catabolic effect on endocortical bone and anabolic effect in cancellous bone.[13-15] This form of severe bone disease has been replaced with mild disease characterized by osteoporosis and decreased bone density and has become the most common indication for parathyroidectomy in many series.[3] Recovery of bone mass and complete regression of bone lesions have been documented following successful parathyroid surgery in many series.[16-18] We relied on the alkaline phosphatase enzyme returning to normal as an indication to bone healing which might take several months following surgery in severe cases. Hypovitaminosis D leads to hyperparathyroidism, increased bone turnover and bone loss and can increase the severity of bone diseases in 1HPT.[19] The prevalence

Table 1 - Duration of symptoms before diagnosis.

Duration in years	n of patients
>4 years	14
3-4 years	7
2-3 years	7
<2 years	12

Table 2 - Differentiation between primary hyperparathyroidism and metastasis or multiple myeloma.

Parameter	1HPT	Metastasis or multiple myeloma
PTH	High	Low
Calcium	High/normal	High/normal
PO_4	Low	Normal
CI	High	Normal
ESR	Normal	High

PO_4 - serum phosphorus, CI- serum chloride, PTH - parathyroid hormone, 1HPT - primary hyperthyroidism, ESR - erythrocyte sedimentation rate

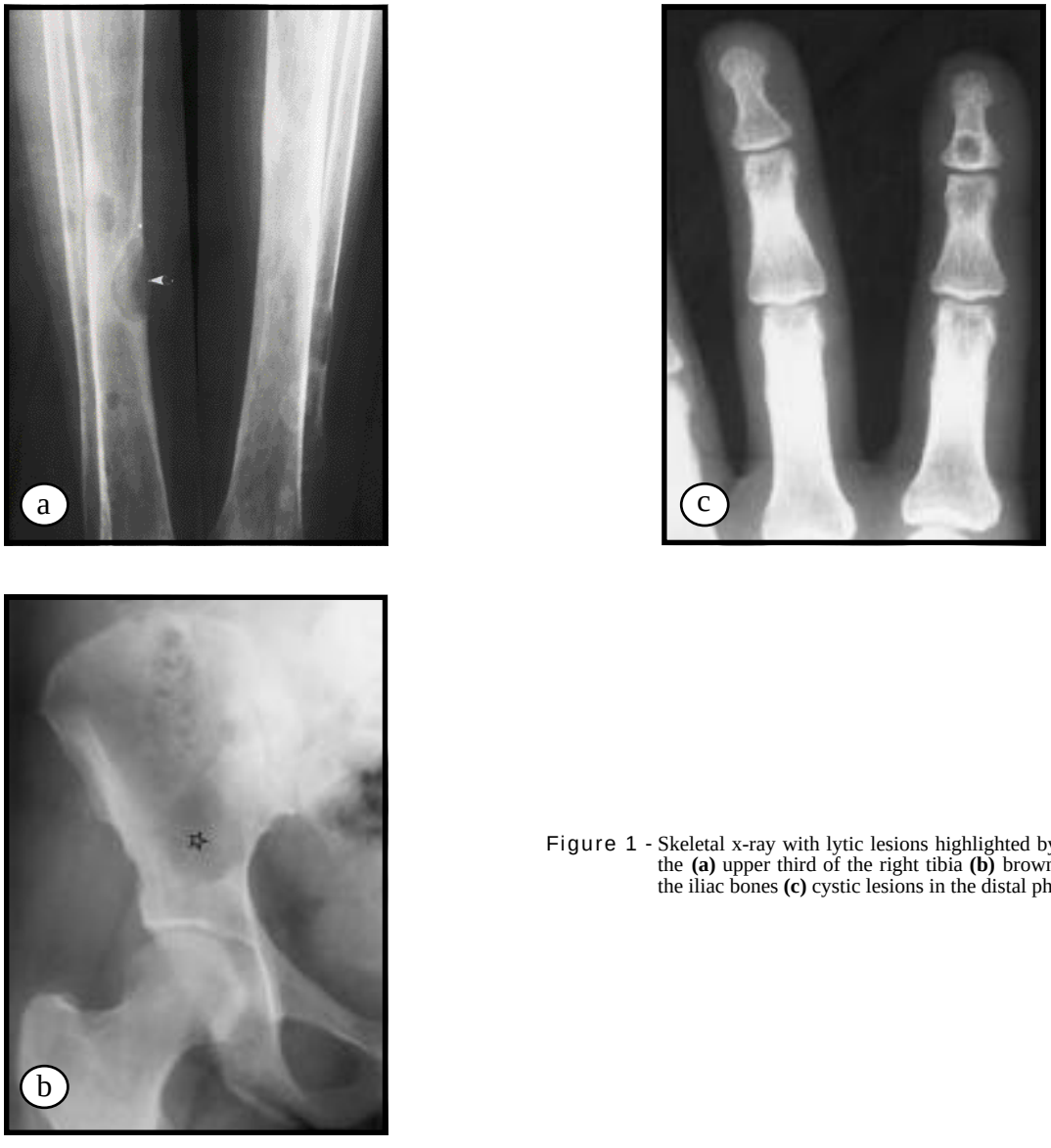

Figure 1 - Skeletal x-ray with lytic lesions highlighted by arrows in the **(a)** upper third of the right tibia **(b)** brown tumors in the iliac bones **(c)** cystic lesions in the distal phalanx.

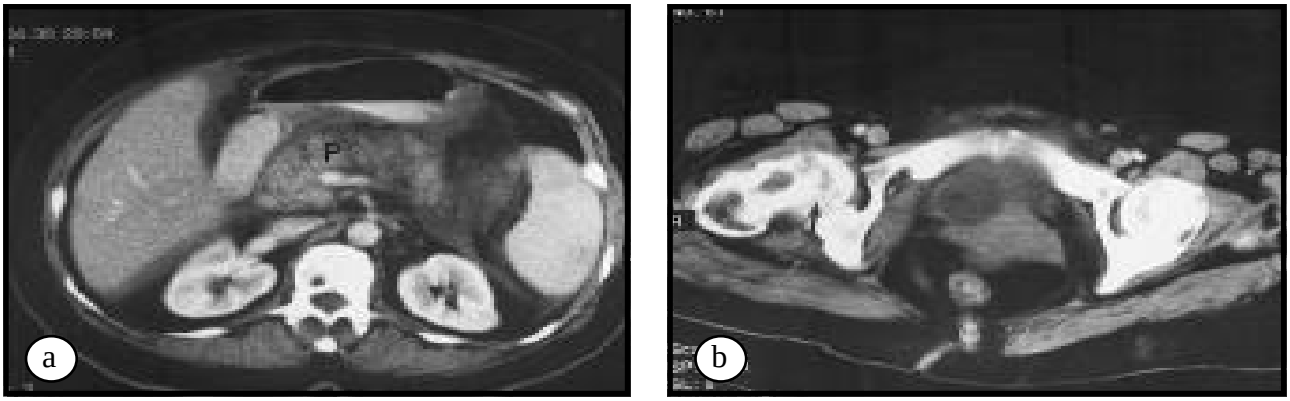

Figure 2 - Computerized tomography of the abdomen showing **a)** acute pancreatitis secondary to hypercalcemia and **b)** fractured right femur.

of hypovitaminosis D was 62.3% in healthy young Jordanians[20] and reaches up to 72.8% in Lebanese volunteers.[21] We did not measure the level of Vitamin D in our patients. Nonetheless, these data do raise an important question: Is hypovitaminosis D, that is common in our part of the world responsible for the marked severity of bone disease seen in our patients? Further, studies are required to answer this question and, subsequently to determine the need for new therapeutic guidelines. Consistent with what is reported in the literature, 10 patients in our series presented with renal stones the disease was controlled in 8; one patient continued to have troubles with stone formation. And one patient presented with acute renal failure due to severe hypercalcemia. Renal disease is seen in 18-36% of the patients with 1HPT.[7,22,23] The disease can influence both renal structure and function. It is more commonly seen in young male patients who tend to present in a recurrent symptomatic colics even with mild hypercalcemia whereas in elderly individuals it presents as an incidental findings on an x-rays.[22,23] Renal stone formation ceases after successful parathyroid surgery and recurrent renal stone formation is a definite indication for parathyroid surgery even in the marginally hypercalcemic patient.[8,9,22,23]

Generalized weakness and muscle ache was seen in 14 patients in our series. In 4 patients, the disease was so severe to the extent that they were confined to bed unable to walk. All of these patients reported marked improvement and managed to walk normally few months after parathyroidectomy. The large majority of patients with neuromuscular symptoms have reported rapid improvement following parathyroidectomy.[24-26] The incidence of non-specific abdominal symptoms ranges from 5-20% of patients with 1HPT.[2,3,7] Severe pancreatitis was seen in one patient in this series. The same patient has also fractured neck femur and severe hypercalcemia. This is in contrast to what one would expect in pancreatitis. The patient underwent uneventful recovery after parathyroidectomy **(Figures 2a & 2b)**. The reported incidence of asymptomatic hyperparathyroidism ranges from 2-80% of individuals with 1HPT.[2,3,5] Although, many if not all patients with asymptomatic 1HPT if carefully evaluated will show many symptoms related to hyperparathyroidism.[22] Indeed vague psychiatric, generalized weakness, and neuromuscular symptoms may only be fully appreciated in retrospect, once the patients has been cured by surgery. Following successful parathyroidectomy approximately 50% of those patients experienced substantial relief from pre-operative symptoms.[23-26] Only one patient in our series was discovered incidentally during routine work up and considered to be asymptomatic with regard to hyperparathyroidism. Our strategy for 1HPT is to identify all 4 parathyroid glands. Once parathyroid adenoma is identified, surgical excision is performed followed by systematic exploration of all the other parathyroid glands. Should hyperplasia be raised by gross and frozen section evaluation, or both, subtotal parathyroidectomy leaving a well vascularized remanent 40-50 mg is performed or auto implantation of one parathyroid in the forearm. Each thymic tongue also should be excised routinely as part of this procedure.

Unilateral exploration of parathyroid gland has been recommended by some authors, proponents of this policy state that this method saves intraoperative time, is associated with less hypoparathyroidism and nerve injuries and that reoperations are easier due to the 2nd side was never touched.[27-31] Many problems are associated with unilateral exploration. These include failure of recognizing hyperplasia in around 10% of the cases and double adenoma in around 5-9% of cases in some series.[6,7,32] Many studies have documented a

success rate of 95-98% in patients with pHPT with a low incidence of complications <1%.[5-8] In our series. The success rate is 97.5%. Calcium and Vitamin D should be used liberally when necessary in all patients to prevent hypocalcemia in the post operative period.

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