CARCINOMA OF THE PARATHYROID

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SINCE THERE HAVE been only 10 cases of carcinoma of the parathyroid with metastases previously reported in the literature, it is considered appropriate to present a new case with metastases. The subsequent course and autopsy findings of a case, previously reported as an adenoma with local recurrence, which developed metastases, is also presented. This makes a total of 12 cases of carcinoma of the parathyroid with metastases reported in the literature. In addition, the remainder of the history of a previously reported case of carcinoma which was ameliorated by radiation, is detailed. The 20 cases in the literature, which are believed to be carcinoma, are tabulated and analyzed in an attempt to determine the course and prognosis of this disease. Certain prophylactic and therapeutic points in the management of tumors of the parathyroid are indicated.

Cases reported as carcinoma of parathyroid that did not have hyperparathyroidism are not included in the discussion, although obviously nonfunctioning malignant tumors may arise in the parathyroid glands as they do in other endocrine glands. The criteria for the diagnosis of carcinoma of the parathyroid have not been fully established. The diagnosis cannot be made on the basis of cellular pleomorphism and giant nuclei. Figure 1 is an adenoma from a case followed for over 20 years to death of the patient without subsequent recurrence of symptoms. The presence of small clumps of tumor cells lying free within blood vessels or incorporated within the capsule of the tumor have previously been indicated as a criterion of carcinoma, but this is not justified. An unequivocal diagnosis of carcinoma can be made only if metastases are found, either at the time of the original operation or at a later date (Table I). It is believed, however, that a tumor which is densely adherent or locally invasive at the time of the original operation and subsequently recurs, also is carcinoma (Table II).

It must be remembered that benign tumors of the parathyroid occasionally occur within the thyroid, and in some instances a capsule does not form. This results in the appearance of invasion and has led to the erroneous diagnosis of carcinoma. The diagnosis of carcinoma in those cases in which the tumor was densely adherent at the time of the original operation but has not subsequently recurred is equivocal, but they will be considered as carcinoma in this discussion (Table III). It is of interest to note the parallelism between parathyroid tumors and those of other endocrine origin, particularly thyroid, adrenal cortex and pancreas. It is not rare to see tumor cells lying free within the vessels in these three areas. A capsule is usually not formed in islet cell adenomas and giant nuclei are often present in adrenal cortical tumors.

* The opinions contained in this paper are those of the author. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department. Submitted for publication October, 1953.

Those tumors reported as carcinoma which were not invasive and did not recur,[2, 23, 24, 26] those in which spillage of the tumor occurred at the original operation and local recurrence was cured by subsequent operation,[21, 27] and the one case in which a portion of tumor was transplanted subcutaneously to avoid tetany,[7] are not considered as carcinoma. Norris[20] reported a case as that of Kilgore and Taylor, but it was originally and subsequently reported by Black.[5] The Massachusetts General Hospital Case #37091[17] is not included, since it was so at variance with the other cases of this series, and since there is reasonable doubt of the diagnosis.

DISCUSSION

The median age of the patient with carcinoma was 38.5, and the average age was 41. This is somewhat younger than the median and average age of those with adenomas. The incident ratio of men to women was 11 to 9 and at marked variance with the ratio of 1 to 3 in adenomas.[19]

Nine cases presented with the nonspecific symptoms of hyperparathyroidism, and three others developed such signs and symptoms early in the course of the disease. In the others, the history was dominated by the complications of hyperparathyroidism. Eighteen of the 20 cases of carcinoma presented with or developed early in their course lesions of bone. In the other two cases the course of the illness prior to operation was very short. In one of these the diagnosis was established on the basis of hyperparathyroidism alone, and the other on the basis of chemical studies done during treatment for renal calculi. Only five had a history of renal lesions associated with the bone disease prior to original operation. Three had nephrocalcinosis, and two had renal calculi. This is in marked contrast to hyperparathyroidism caused by adenomas, since in those instances the renal lesions cause the symptoms which most commonly lead to the diagnosis of hyperparathyroidism. With persistence and progression of the disease, kidney lesions become much more common. Nephrocalcinosis was present in eight of the ten cases in which necropsy was performed. One of the others was said to have chronic glomerulonephritis, and one died immediately after her second operation, with acute hyperparathyroidism. One had a history of an operation for duodenal ulcer eight months prior to development of symptoms of hyperparathyroidism, an association previously noted with parathyroid adenomas. One had acute pancreatitis terminally and one a chronic pancreatitis during the course of the illness, an unexplained high incidence of association of disease.

The side of the neck where the lesion was located was stated in 17 cases. Of these, eight occurred on the right and nine on the left. In the eight cases that indicated a more specific site four were found in the area of the right, and four in the area of the left, lower pole of the thyroid. This coincided remarkably well with the location of adenomas in a large series since they were divided approximately equally as to side of the neck, but showed a marked predilection for the area of the lower poles of the thyroid. The volume of the carcinomas at the time of the original operation was approximately three times that of a series of 322 cases of adenomas.[19] The large size is responsible for these tumors being much more frequently palpable prior to operation.

The gross diagnosis frequently presents a difficult problem. There are several findings which are helpful. In ten cases of this series the original tumor was described as locally invasive or adherent to the surrounding structures. In four of these, a large mass completely surrounded the recurrent laryngeal nerve. When such a finding is noted at operation there is little doubt of the diagnosis of carcinoma. In

TABLE I. *Parathyroid Carcinoma. Cases with Metastases.*

Author	Sex Age Of Onset (Yrs.)	Presenting Symptoms & Original Diagnosis	First Operation: Size (mm.) and Local Characteristics	First Operation: Location and Microscopic* Characteristics	First Operation: Relief of Symptoms (mos.)	Second Operation: Size (mm.) and Local Characteristics	Second Operation: Location and Microscopic* Characteristics	Second Operation: Relief of Symptoms (mos.)	Follow-up and Total Duration of Disease (mo.)	Autopsy & Remarks
Gentile *et al.*	M 36	Hyperparathyroidism Osteitis fibrosa cystica. Osteoporosis	50 x 30 x 20	Region of left lobe.	2	8 x 11	Cervical gland left side neck.	60	Dead† 87	Autopsy: Chronic glomerulonephritis, cardiac hypertrophy, bronchopneumonia.†
		Adenoma (malignant)	Densely adherent	2+ Invasion of vein wall.		Enclosed in scar tissue.	2+ Tumor cells in vascular spaces.			
Bertrand-Fontaine & Moulonguet	F 45	Hyperparathyroidism Osteoporosis. Osteitis fibrosa cystica.	.....	.....	12	Almond	In operative scar.	0	Dead 71	Third operation radical resection. Hemithyroidectomy. Mass extended into mediastinum. 6 months later local recurrence in neck.
		Adenoma	.....	1+ Alveolar. Very few mitosis.		Densely adherent to deep planes.	3+ Numerous mitosis.			X-ray treatment, no relief. Autopsy: Tumor in thyroid, lung, nephrocalcinosis, osteoporosis.
									Dead 44	X-ray treatment—no effect. Autopsy: Tumor in upper pole left lobe thyroid adjacent to right jugular vein. Metastases to lymph nodes, lungs & right kidney. Osteitis fibrosa cystica. Multiple pathological fractures. Nephrolithiasis. Nephrocalcinosis.
Meyer & Ragins	M 56	Osteitis fibrosa cystica. Hpyerparathyroidism	60 x 50 x 45	Right side	8					
		Non-hornifying squamous cell carcinoma.	.....	3+ Cyst up to 15 mm.						
Black & Haynes	F 49	Osteitis fibrosa cystica.	(1) 28 x 26 x 18	(1) In right lobe.	12	.....	(1) Below right lobe.	28	Dead 84	No autopsy.
		Hyperparathyroidism	(2) 18 x 15 x 8	(2) Below infer. pole.			(2) Right deep jugular region.			Clinical diagnosis: Bronchopneumonia; uremia.
		Malignant	.....	3+		(1) Infiltrating partially fixed. (2) 3 nodes.	3+			
Mass. Gen. Hospital 34491	F 38	Hyperparathyroidism Osteitis fibrosa cystica.	25 in diameter	Lower right.	12	Biopsy	Left side.	0	Dead† 39	Third operation: "Adenoma" from mediastinum.
		Carcinoma.	.....	3+		Invasion	3+			Fourth operation: Tumor in lymph node on left & right side of neck & mediastinum.† No autopsy. Clinical diagnosis: Uremia.†
King & Wood	F 37	Osteoporosis. Osteitis fibrosa cystica.	40 x 30 x 30	Lower left	28				Dead 69	X-ray treatment—no effect.
		Adenoma	.....	2+						Autopsy: Metastases to lungs. Nephrocalcinosis & nephrolithiasis. Osteoporosis & osteitis fibrosa cystica.
von Albertini	M 45	Osteitis fibrosa cystica.	Hazel nut	Lower pole left lobe.	48	10	Lower pole left lobe.	0	Dead 60	Third operation: Pea-sized nodule left paratracheal region. Invasion of small nerve. Died 5th postoperative day.
		Adenoma	.....	1+		.....	2+ Invasion of capsule.			Autopsy: Osteitis fibrosa cystica, spontaneous fracture femur, thrombosis of pelvic and leg veins, massive lung embolism, nephrocalcinosis, left hydronephrosis and renal calculi, and walnut-size metastases in liver.
Stephenson	M 57	Ostietis fibrosa cystica. Osteoporosis. Renal calculi.	20 in dia.	Region of left lobe.	15	3 pieces, largest 10 x 10 x 15	Left lobe.	0	Dead 26	Autopsy: Tumor 32 x 22 x 15 mm. firmly attached to trachea posterior to lower half of left lobe. Surrounded left recurrent nerve. Tumor 17.5 mm. over posterior surface of left lobe and 2 mm. in diameter in thyroid. Osteitis fibrosa cystica; nephrocalcinosis; renal calculi; paralyses of left recurrent, perirenal abscess; pyelonephritis; meningitis; acute bacterial endocarditis; chronic pancreatitis.
		Adenoma	Intimately connected with lower pole.	1+		Tumor cells between muscle fibers.	1+			
Black & Ackerman	F 56	Osteitis fibrosa cystica.	(1) 20 x 15 x 15 (2) Larger than 20 x 15 x 15 (3) Lymph node 10 x 10 x 5	Behind right lobe.	10	.....		0	Dead 51	X-ray with improvement. No autopsy. Clinical diagnosis: Uremia.
		Carcinoma	.....	2+ Tumor emboli in vessels.		1 hyperplastic parathyroid.				
Black & Ackerman	M 16	Osteitis fibrosa cystica.	20 in dia.	Posterior to right lower lobe.	60	(1) 15 in dia. (2) 2.5 in dia.	(1) Right lower pole. (2) Right upper pole.	102	Dead 180	Hemithyroidectomy.
		Adenoma	.....	1+ Tendency to spindle shape			3+ In thyroid & muscle. Cystic.			Autopsy: Tumor 20 x 35 x 20 right side of trachea. 4 mm. nodule upper pole of left lobe thyroid. Several 4–10 mm. nodules, neck & upper mediastinum Several 10 mm. lymph nodes in upper mediastinum. Metastatic calcification of smooth, striated and heart muscle and kidneys. Pyelonephritis, bronchopneumonia, acute pancreatic necrosis.
Ellis & Barr	F 23	Hyperparathyroidism Osteitis fibrosa cystica. Giant cell tumor.	2 tumors	left side	30	(1) 20x15x15 (2) 15 x 10 x 5 (3) 12 x 10 x 5	.....	0	Dead 72	Third operation: 2 small nodules within left lobe thyroid. Hemithyroidectomy. Fourth operation. 2 nodules 9 x 12 mm. from upper & lower lobes lung.
		Adenoma	.....	1+		.....	.....			Autopsy: Metastases to liver, lymph node, muscle & lung. Metastatic calcification of lungs, kidneys, stomach, arteries & heart. Osteitis fibrosa cystica.
Black, V. K.	M 37	Hyperparathyroidism Osteitis fibrosa cystica. Nephrocalcinosis	30 x 20 x 20	Left lower lobe.	4	(1) 10x20x20 (2) 5 x 10 x 10 node.	Beside trachea left lower post. border of sternocleido muscle behind manubrium.	1	Well 21	X-ray therapy.
		Carcinoma		2+ Blood vessel & fat invasion		(3) Mass obviously carcinoma.				

*An estimate of cellular pleomorphism from information furnished by the description and illustrations.
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TABLE II. *Parathyroid Carcinoma. Cases Locally Invasive at Original Operation and with Recurrence.*

Gutman	M 56	Osteitis fibrosa cystica.	45 long.	.....	15	.....	.....	Moderate	Dead 36	No autopsy.
		Carcinoma.	Invading thyroid.	Invasion of blood vessels.		Obviously carcinoma.	.....	.....		
Young & Emerson	F 39	Hyperparathyroidism Osteoporosis. Osteitis fibrosa cystica.	30 x 35	Posterior to left left lobe.	36	35 x 25 x 25	Beneath left sternocleidomastoid muscle.	0	Dead 240	Hemithyroidectomy. Autopsy: Metastatic calcification of arteries. Arteriolonephrosclerosis. Acute hyperparathyroidism.
		.....	Adherent to thyroid. Surrounded recurrent nerve.	1+ Several cysts.		Adherent to larynx and esophagus.	1+			
DeGennes *et al.*	M 38	Hyperparathyroidism Osteitis fibrosa cystica. Carcinoma	38 x 33 x 24 Adherent	Posterior to left lobe. 1+ Blood vessel & lymphatic infiltration at a distance. Satellite nodules. Invasive.	10				Dead** 17+	Operated 8 months previous for duodenal ulcer. Hemithyroidectomy. No autopsy. Clinical diagnosis: Local recurrence, hyperparathyroidism, uremia.†
O'Donovan	M 26	Hyperparathyroidism	Half a walnut	Anterior and inferior aspect of left lobe.	12	Weight 3.5 gms.	Site of previous operations.	0	Dead 24	Hemithyroidectomy. No autopsy.
		Carcinoma*(?)	Adherent to thyroid, esophagus & trachea. Surrounding recurrent nerve.	2+		Invading esophagus over extensive area.	2+			Clinical diagnosis: Subacute parathyroid intoxication.

*An estimate of cellular pleomorphism from information furnished by the description and illustrations.
†Personal communication with the author.

TABLE III. *Cases Locally Invasive at Original Operation and Without Recurrence*

Fretheim & Lange	M 37	Osteitis fibrosa cystica. Osteoporosis. Hyperparathyroidism. Nephrocalcinosis.	Pigeon egg.	Right lower.	72+				Well† 96	Hemithyroidectomy. No sign of recurrence.†
		Carcinoma.	Adherent. Surrounding recurrent nerve.	2+ Infiltrating muscle, fascia, thyroid.						
Maruelle	F 50	Osteitis fibrosa cystica. Osteoporosis.	50 x 35 x 20	Posterior to right lobe.	36				Well 72	Radical removal, readily separated from thyroid.
		Carcinoma.	Adherent Surrounding recurent nerve.	4+ Capsule.						
Anderson & McWhorter	M 35	Hyperparathyroidism. Osteoporosis. Nephrocalcinosis.	Autopsy* (1) 50 x 40 x 30 (2) 4 satellite nodules up to 8 mm.	Posterior to right lobe.	0				Dead 8	Autopsy: Metastatic calcification myocardium, coronary arteries, lungs-kidneys and stomach. Acute hyp r, parathyroidism.
		Autopsy: Carcinoma	Lymphatic permeation.	1+						
Woolner *et al.*	F 43	Renal calculi. Chemical hyperparathyroidism.	10 Gm. Extensive invasion of nerve, muscle, & thyroid.	.....	18				Well 24	Radical removal.
		Carcinoma		1+						

*An estimate of cellular pleomorphism from information furnished by the description and illustrations.
†Personal communication with the author.

three other cases, more than one associated mass was present. This could possibly be confused with multiple adenomas, with secondary hyperplasia, or with primary hypertrophy and hyperplasia, but the diagnosis of carcinoma should be strongly suspected. A large presenting mass should also evoke a suspicion of carcinoma.

The microscopic appearance is quite confusing at times because an adenoma may show extremely pleomorphic cells and nuclei, giant cells, nests of cells within the surrounding capsule and small nests of tumor cells lying free within blood vessels. Castleman[8] feels that all tumors of the parathyroid that show mitotic figures are carcinoma, no matter how infrequent the mitoses.

Mitoses were described in 14 of the 20 accepted cases in the literature. In three cases, a definite statement of absence was made. Castleman also feels that a trabecular arrangement of the tumor cells is significant in the diagnosis. In 14 cases a description of the cellular arrangement was noted. Six were described as sheets or solid and seven were said to be of alveolar, acinar, perithelial or anastomosing cord

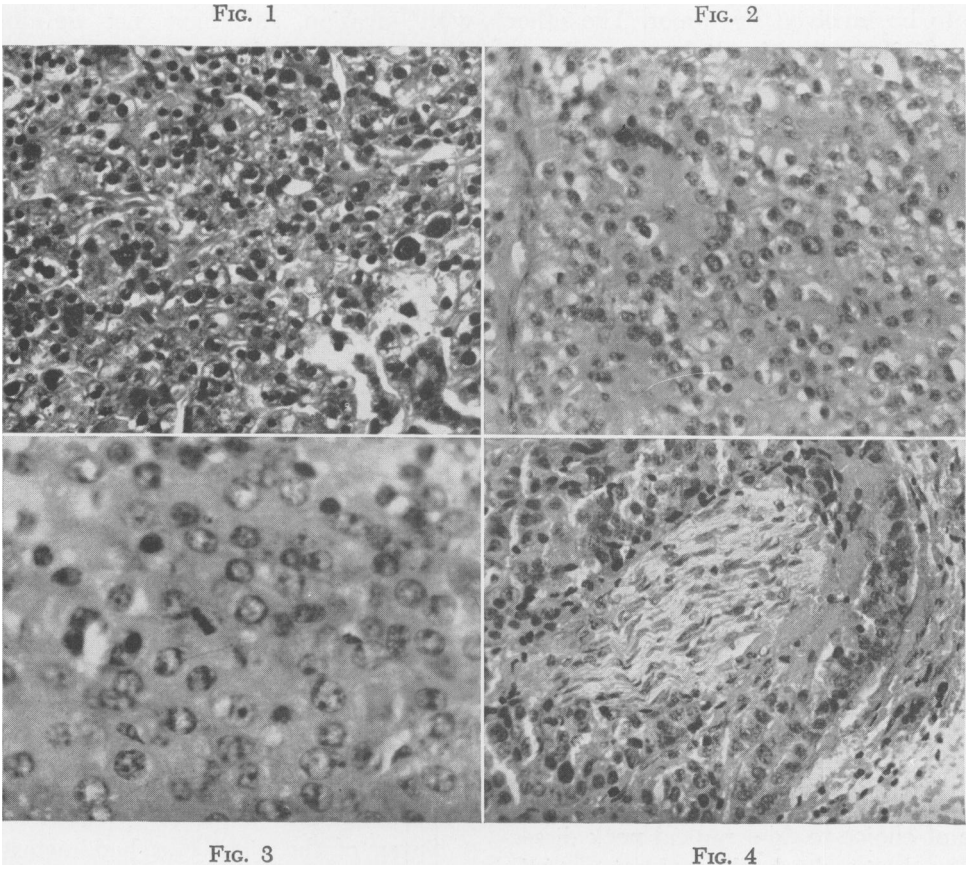

FIG. 1. Photomicrograph of an adenoma showing pleomorphism. This is not significant in the diagnosis of carcinoma (120 x).

FIG. 2. Photomicrograph of carcinoma showing uniform transitional cells with perithelial arrangement in Case 1 (120 x).

FIG. 3. Photomicrograph of mitotic figure in Case 1. This is diagnostic of carcinoma of parathyroid (300 x).

FIG. 4. Photomicrograph showing perineural lymphatic invasion in Case 1 (120 x).

arrangement. One had both types of configuration.

Six of the 12 cases with metastases were diagnosed as carcinoma originally. In three of these the diagnoses were established on the basis of cellular pleomorphism and in three cases the blood vessels were considered to be involved by tumor. The other six cases showed only slight to moderate pleomorphism and were diagnosed as adenoma. Seven of the eight locally invasive neoplasms were stated to have been recognized as carcinoma at the original operation; in the other, no statement was made.

Six of the cases which were locally invasive at the original operation were treated with radical surgery. Three of these, including one that had a hemithyroidectomy, are well an average of 41 months following operation. The other three, in spite of radical surgery, including hemithyroidectomy, had recurrence of symptoms an average of 19 months later. It is imperative that all the tumor is removed at the original operation. To do so will often require radical surgery including a hemithyroidectomy, and sacrificing the recurrent laryngeal nerve. If the tumor presents as a locally invasive process, particularly when it has formed a mass surrounding the recurrent laryngeal nerve, or if lymph node involvement is present, it would probably be the procedure of choice to do a radical neck dissection on the involved side at the time of the original operation. Since the microscopic appearance of the tissue may appear benign, it is dangerous to rely on rapid section diagnosis. At times (*i.e.*, with obvious lymphatic involvement or tumor thrombi in blood vessels or mitotic activity) the pathologist may be able to make the diagnosis of malignancy with considerable confidence. Five of the patients were treated with roentgen therapy; three without benefit, one with improvement and one did not complete his therapy and has not been seen since. However, in the present status of therapy of these tumors, it would be well to give irradiation therapy to any case in which it is possible that the tumor has been incompletely excised.

Relief of symptoms due to the original operation in those cases that had, or later developed, metastases, lasted approximately 20 months. In those cases that presented with invasion and have not developed metastases, excluding one case that died immediately postoperatively, relief of symptoms has been over 28 months. Three of this later group have not developed recurrence and are still alive according to the available information. Obviously this will extend the average duration of relief of symptoms in these cases. Ten of the 12 that developed metastases had a second operation. Six had no relief of symptoms. One case still living has had relief for one month. The other three had amelioration of their symptoms for 28, 60 and 102 months. Three of the four that had invasion at the original operation and later developed recurrence of symptoms, were operated on a second time; two had no relief and one had moderate relief of symptoms. Of the 16 cases that developed recurrence of symptoms, 15 are dead and the other has persistent tumor. The course of the disease of those who have succumbed varied from eight to 240 months, with a median of 55.5 months and an average of 69.5 months.

Seven of the eight that had metastases and were autopsied showed persistent tumor. In two of these there was a mass at the site of the original tumor, and four had tumor nodules within the thyroid. In three cases there was involvement of the regional or mediastinal lymph node. In four cases there were distant metastases to the lung, in two to the liver, and in one to the kidney. In one case direct invasion of muscle was reported. Two of the five cases that developed local recurrence without metastases died of acute hyperparathyroidism and one with subacute hyperparathyroidism. Nephrocalcinosis was present in eight

of the ten cases in which necropsy was performed. One of the others had chronic glomerulonephritis, and one died immediately after her second operation, with acute hyperparathyroidism.

on his left wrist and on the left inferior alveolar ridge of the mandible.

During physical examination the nodules were noted and were believed to be cystic and attached to bone. A mass was palpated in the area of the left lower lobe of the thyroid.

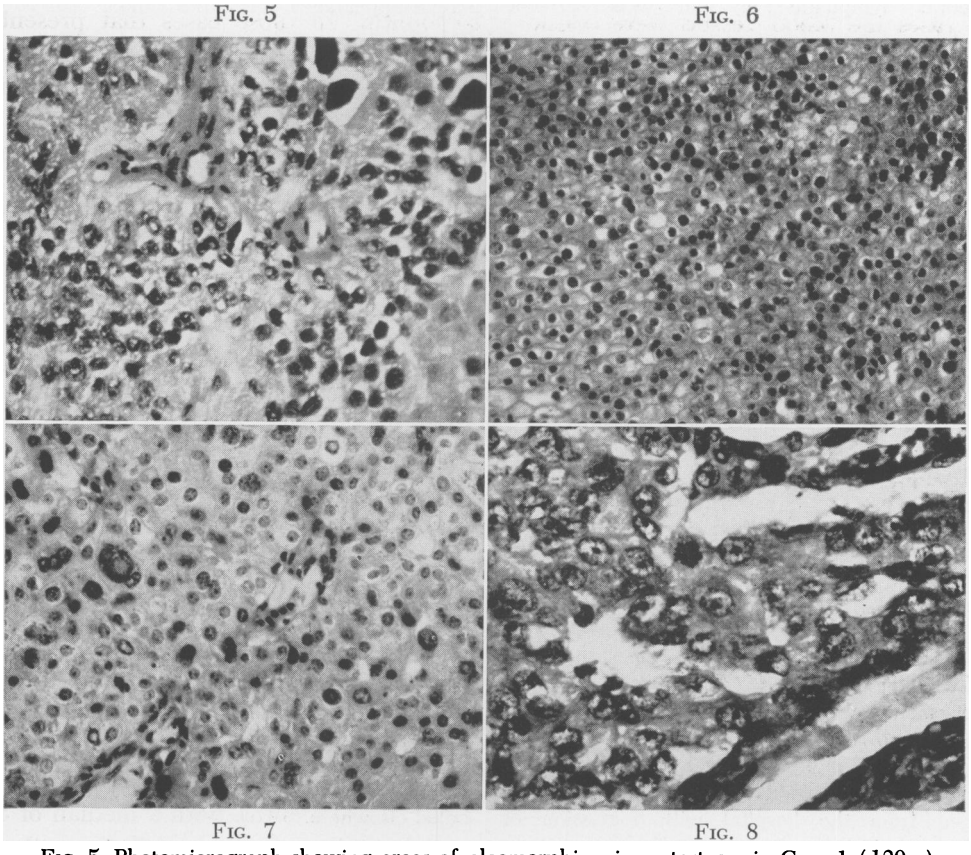

FIG. 5 FIG. 6

FIG. 7 FIG. 8

FIG. 5. Photomicrograph showing areas of pleomorphism in metastases in Case 1 (120 x).
FIG. 6. Photomicrograph showing uniformity of carcinoma that was present in most areas in Case 2 (120 x).
FIG. 7. Photomicrograph of area of most marked pleomorphism in the original tumor in Case 2 (120 x).
FIG. 8. Photomicrograph of mitotic figure in Case 2 (300 x).

CASE REFORTS

Case 1. (*R. F.**) Five years prior to admission this 38-year-old white man developed hypertension. He had most of his teeth removed because they were becoming loose. About 4 months ago he began to notice fatigue, weakness, weight loss and loss of ambition. He also began having sharp pains in his heels, thighs, knees, and occasionally in his back. About 2 weeks ago he noticed a nodule

The hemogram was normal. The urine studies revealed 40 to 50 RBC/HPF and a 3 plus Sulkowitch when he was on a low calcium diet. The blood serum calcium was 21 mg. per cent; the serum phosphorus was 3 mg. per cent, and the alkaline phosphatase was 9 Bodansky units.

Roentgen ray studies showed cystic lesions of the right fourth rib, cystic demineralization of the mandible, osteoporosis with loss of the lamina dura of the teeth, and nephrocalcinosis.

At operation a 3 x 2 x 2 cm. lobular nodule weighing 9 Gm. was densely adherent and was excised from the left lower lobe of the thyroid.

* Dr. Duff Allen, Washington University, St. Louis, Missouri, has kindly given permission to publish this case.

It showed some areas of necrosis and hemorrhage. Microscopically the tumor was composed of transitional cells and chief cells. The tumor cells were quite uniform and closely packed (Fig. 2). Rare mitotic figures were present (Fig. 3). The adjacent thyroid was invaded by tumor cells. Large tumor thrombi were found within the veins and perineural lymphatic invasion was present (Fig. 4).

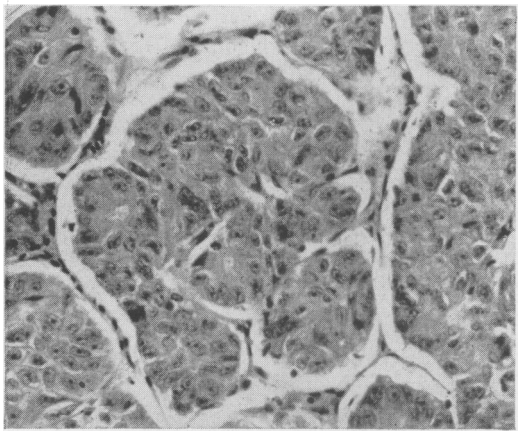

FIG. 9. Photomicrograph of metastases in Case 2 showing marked change in cellular arrangement (120 x).

Following removal of the mass, the blood serum calcium was 12.8 mg. per cent and serum phosphorus 0.79 mg. per cent. The non-protein nitrogen was 36 mg. per cent and the basal metabolic rate was minus 24 per cent. He was discharged from the hospital with regression of symptoms.

He felt quite well for 4 months following the operation. He did have painless gross hematuria, but he passed no kidney stones. His symptoms of backache and leg aches began to recur with increasing severity. The nodule on the left wrist remained the same. Within 8 months these pains became so severe that he was unable to work and he returned to the hospital after being incapacitated for 4 months.

On readmission, a mass, which was moderately tender and moved with deglutition, was palpated at the left lower lobe of the thyroid. No lymph nodes were palpable. The serum calcium was 18.5 mg. per cent and the alkaline phosphatase was 8 Bodansky units.

At operation a 1 x 2 x 2 cm. mass was observed lying on the left side of the vertebrae and adjacent to the trachea. Other masses of firm tissue were felt extending posteriorly to the manubrium to the vessels of the base of the neck and also superiorly toward the skull. A radical neck dissection was started but was abandoned when a ½ x 1 x 1 cm. node containing tumor was found lying at the posterior border of the sternocleidomastoid muscle. A second node was observed. The microscopic appearance was quite similar, except very few transitional cells were noted, the perivascular arrangement was more prominent, and there were areas of pleomorphism (Fig. 5).

On the fourth postoperative day the serum calcium was 16.5 mg. per cent, phosphorus 1 mg. per cent, and alkaline phosphatase 4 Bodansky units.

Roentgen ray therapy was begun on the sixth postoperative day. He received 1600 roentgen to an 11 x 15 cm. field anteriorly; 400 roentgen to an 8 x 15 cm. field to the right side of the neck; and 400 roentgen to an 8 x 15 cm. field to the left side of the neck during the next 24 days. Treatment was not completed because he failed to return.

Comment. The original diagnosis of carcinoma was readily made in this case since there was invasion of the surrounding tissue, tumor thrombi were found in the veins, perineural lymphatic invasion was present, and mitotic figures were noted.

Case 2. (*F. B.*) This case was previously reported[6] as an adenoma, with recurrence following spillage of tumor at the original operation. Subsequently, however, he died and metastases were found at autopsy. The history, to August 29, 1949, will be presented briefly, since it has been detailed elsewhere.

Investigation of the presenting symptoms of progressive knock knee and leg pain in a 16-year-old boy revealed generalized osteoporosis, and the laboratory findings of hyperparathyroidism. During the removal of a tumor, 2 cm. in diameter, from the area of the right lower parathyroid gland, some of the contents were spilled in the operative site. The tumor was composed primarily of chief cells, but there were islands of transitional cells. For the most part the tumor cells were quite uniform (Fig. 6), but scattered throughout were areas of pleomorphism (Fig. 7). An occasional multinucleated cell and mitotic figure were seen (Fig. 8). Postoperative symptoms of tetany responded well to calcium and AT.10

Nine years later he returned, complaining of symptoms of hyperparathyroidism and mild hypertension for the last 2 to 4 years. Blood chemistry and roentgenographic studies were again those of

hyperparathyroidism. At operation tumor nodules, measuring up to 1.5 cm. in diameter, were found at the upper pole on the anterior surface and on the posterior aspect of the lower pole of the thyroid. Hemithyroidectomy was done to facilitate removal of the masses. Microscopically there was considerably more pleomorphism of the tumor and it was located within thyroid tissue and the adjacent muscle bundles. Postoperatively he had a few episodes of mild tetany which were relieved by intravenous injection of calcium gluconate.

Two years after this operation he was seen as an out-patient. He complained only of headaches. The hypertension had gradually increased, but recently had become stabilized at 220/100. Laboratory studies revealed a calcium of 14.4 mg. per cent; phosphorus 2.5 mg. per cent; alkaline phosphatase 15 Bodansky units. Roentgenologic study demonstrated considerable osteoporosis and prominent nephrocalcinosis. Further operative procedures were not done. The remainder of his clinical course is not known.

The autopsy* showed a firm, gray, 20 x 35 mm. mass of tissue on the right side of the trachea, just above the clavicle. This mass was lateral and posterior to the trachea and was impinging upon it at the level of the thyroid cartilage. There was a firm 4 mm. white nodule on the anterior surface of the upper pole of the left lobe of the thyroid. In addition there were several 4 to 10 mm. nodules extending downward into the upper mediastinum. Several lymph nodes, 10 mm. in diameter, in the upper mediastinum contained firm, gray nodules. Microscopically few transitional cells were present, lobulation by connective tissue was prominent, mitotic figures were more common, and pleomorphism minimal (Fig. 9).

The autopsy also revealed extensive metastatic calcification of smooth, striated, and heart muscle and of the kidneys. There was also pyelonephritis, bronchopneumonia, and acute pancreatic necrosis.

Comment. This case emphasizes the necessity for complete removal of the tumor at the original operation. It was unfortunate that the capsule was perforated in this instance.

This case also illustrates the long period of time that may elapse before recurrence of tumor and symptoms. In this case it was five years, although in one case symptoms recurred after only two months.

* The autopsy findings were reported through the courtesy of Dr. G. V. Miller, St. John's Hospital, Springfield, Missouri.

Case 3. (S. D.) The course of this case, to 1950, has been previously presented.[6] The remainder is detailed here.

This 56-year-old woman first complained of back pain. Roentgenographic studies of the spine and skull showed marked osteoporosis. Blood calcium was 18 mg. per cent; phosphorus 3.3 mg. per cent; alkaline phosphatase 27.5 Bodansky units.

At operation two intimately related adherent masses were found behind the right lobe of the thyroid. The larger mass had infiltrated the prevertebral fascia across the midline, the jugular vein, and the tissues extending into the mediastinum. In addition, a lymph node completely replaced by tumor was found at a distance from these two masses. Microscopically the tumor was composed of bizarre chief cells which showed little pleomorphism. Rare mitotic figures were found. Tumor emboli almost completely filling the lumen of some vessels were present. Over the next 3 years she had persistence of disease ameliorated up to 9 months by radiation therapy to cervical area.

In 1950, bony lesions of the eighth and ninth ribs on the left were found. Irradiation was given to the mediastinum. At that time the calcium was 16 mg. per cent and the phosphorus 2.3 mg. per cent. By April 17, 1951, she gave the history that she tired rapidly, tended to fall asleep easily, was more sensitive to cold, and had frequency and nocturia. Her skin was dry and scaling and her face was a little puffy. The blood calcium was 17.5 mg. per cent, the phosphorus 3.4 mg. per cent and the alkaline phosphatase 8.8 Bodansky units. A 24-hour urinary calcium was 650 mg. per cent. It was felt that she might also have myxedema in addition to the hyperparathyroidism. However, the basal metabolic rate and protein-bound iodine values were within normal range.

She was given thyroid extract and showed a favorable response. Renal function studies were done and showed marked diminution in renal function. It was felt that re-exploration of the left side of the neck was indicated on the basis that compensatory hyperplasia of the remaining parathyroids may have existed. One fairly large hyperplastic parathyroid was removed. There were no masses in the superior mediastinum, but there was extensive scarring, presumably from irradiation. Portions of the thyroid gland and numerous cervical lymph nodes were studied, but no recurrent neoplasm could be found.

The patient was readmitted in June, 1951, complaining of symptoms similar to those mentioned above. Prior to returning to the hospital she had been on cortisone, 12½ mg. per day for 6 days, with no alteration of the recently developed

mental depression. On return to the hospital the blood urea nitrogen was 21 mg. per cent; creatinine, 2.5 mg. per cent; calcium, 19.5 mg. per cent; phosphorus, 3.8 mg. per cent; and alkaline phosphatase, 12 Bodansky units. The urinary calcium was 338 mg. in 24 hours, approximately half that of the previous admission. It was believed that she was gradually developing renal failure, chronic acidosis and possibly secondary hyperparathyroidism.

She was again discharged, to be followed as an out-patient. Before returning she died, apparently in uremia, in August, 1951. Every attempt to obtain an autopsy failed.

Comment. This is the only one of five cases with roentgen ray therapy that had regression of symptoms. In one of the other cases there has not been a sufficient lapse of time to determine whether there will be any evidence of improvement.

CONCLUSIONS

1. A new case of carcinoma of the parathyroid with metastases is presented.

2. The remainder of the history of a case previously presented as a recurrent adenoma, that subsequently developed metastases, and the completion of the history of a case of carcinoma of the parathyroid that showed transient response to roentgen therapy are presented.

3. Pertinent facts from 12 cases of carcinoma of parathyroid with metastases, four cases with local invasion and recurrence, and four cases with local invasion without recurrence are tabulated.

4. Grossly, carcinoma of the parathyroid may be diagnosed if there is local invasion of the surrounding tissues or metastatic disease, and strongly suspected if more than one mass is present or if the presenting mass is large.

5. Microscopic diagnosis cannot be made on the basis of pleomorphism, small nests of tumor cells in the blood vessels, or apparent invasion in the capsule. The presence of mitotic figures, a trabecular pattern, tumor thrombi and lymphatic invasion, are reliable criteria.

6. If invasion by carcinoma of parathyroid is present at the original operation, it is imperative to remove all the tumor by radical surgery, and a radical neck dissection of the involved side should be considered.

7. If a carcinoma of the parathyroid has been inadequately removed, irradiation therapy is indicated.

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