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Studies on the Non-adenomatous Glands in Patients with a Solitary Parathyroid Adenoma

STEN EJERBLAD, LARS GRIMELIUS, HENRY JOHANSSON and IVAR WERNER

From the Departments of Surgery, Pathology, and Internal Medicine, Uppsala University, Uppsala, Sweden

ABSTRACT

The properties of the non-adenomatous glands in 22 cases of primary hyperparathyroidism due to solitary adenoma were studied. The mean glandular and parenchymal cell weight was somewhat lower than that found by others in glands from euparathyroid subjects. In almost all glands the dark chief cells predominated. This cell type indicates endocrine activity. With some exceptions the glandular endocrine activity seems to be less pronounced than in the concomitantly resected adenoma. Histologically there was no apparent signs of atrophy or hyperplasia in the nonadenomatous glands. The clinical relevance of the findings is discussed.

INTRODUCTION

It is a well-known fact that the diagnosis of primary hyperparathyroidism (HPT) has been more and more common during the last decades. It is also apparent that the clinical aspects have changed thoroughly, e.g. nowadays we suspect HPT not only in patients with "bone and stone" disease but also in patients with mental disturbances, neurological disorders, gastrointestinal dysfunction etc.

Within recent years the surgical and histopathological aspects have also changed. Relatively more cases of parathyroid hyperplasia are diagnosed. (2, 3, 6, 13, 14, 16). It has actually been suggested that hyperplasia and adenoma sometimes occur together (2, 17).

The present paper reports observations on 22 patients with typical primary HPT due to solitary parathyroid adenomas. The aim of this study was to examine in particular the non-adenomatous parathyroid glands with regard to weight, cellular composition and structure and to find out if these glands differ histologically from evidently euparathyroid glands. In addition the weight and various histological factors in the adenomas and non-adenomatous glands were correlated.

MATERIAL

The material consists of 22 cases (16 females, 6 males) fulfilling the clinical and chemical (serum Ca >5.2 mEq/l) criteria of primary HPT and operated during 1970–71. The mean age for the females at operation was 52.9 years (range, 31–68 years) and for males 50.1 years (range, 29–68 years). All proved to have a solitary parathyroid adenoma and all were clinically and chemically cured by the operation. No patient suffered from renal insufficiency. There have been no recurrences.

METHODS

The surgical procedure comprised dissection and inspection of all four glands, removal of the adenoma together with removal of or partial resection of 1 or 2 of the other glands. When differences in size were noted on inspection of the 'normal' glands, the largest was always removed.

The specimens were weighed and depending on size divided into suitable pieces, which were fixed in 10% neutralized formaldehyde for 24 hours. After dehydration and clearing in xylene the specimens were embedded in paraffin and sectioned.

The non-adenomatous glands were sectioned throughout into series of 5 consecutive 5 μm thick sections with intervals of 150 μm between each series.

The adenomas were sectioned in 3 to 5 series of 5 consecutive 5 μm thick sections with intervals of 300 to 500 μm between each series.

The sections in the different series were stained with haematoxylin and eosin, the van Gieson stain,

periodic acid Schiff (PAS) with and without previous diastase digestion and with the Grimelius' silver nitrate stain (9).

The amount of adipose tissue and the frequency of the different parenchymal cell types was semi-quantitatively evaluated through microscopical examination of *all* the haematoxylin-eosin stained sections of each gland. The results were expressed as per cent fat tissue of the total gland volume and per cent cells of the total number of parenchymal cells belonging to one cell type, respectively, to the nearest 10%.

A rough estimation of the parenchymal cell weight in the non-adenomatous glands was also made using the formula advised by Gilmour & Martin (7).

$$\frac{1.1 \cdot x \cdot y}{110 - 0.2z + 0.002yz}$$

where x=total weight of the gland; y and z=per cent parenchymal and fat tissue, respectively. The specific gravity of fat was taken as 0.9 and for the remaining tissue as 1.1 (see Gilmour& Martin 1937).

Correlations were tested for weight, amount of fat, parenchymal cell type and structural arrangement, frequency of PAS-positive and argyrophilic cells.

Karyometry

The largest haematoxylin-eosin stained section from each adenoma and non-adenomatous gland was photographed in black and white. On the photographs which had a final magnification of ×550 the surface areas of 200 randomly selected cell nuclei were calculated with the aid of a particle area analyser (Zeiss TGZ 3). The nuclear diameter was calculated from these area-figures. No distinction was made between the different cell types. All nuclear measurements were carried out by one assistant.

RESULTS

Non-adenomatous glands

The mean weight for the 22 non-adenomatous glands was 27 mg, with a range from 15 to 60 mg. The mean parenchymal weight was 18.9 mg with a range from 6.4 to 31.1 mg.

All the glands contained fat tissue, the amount of which varied for females between 10% and 80% and for males between 20% and 50% of the glandular volume. The amount of fat also often varied between different parts of the same gland. The parenchymal cells were arranged in cords, sheets and rare acini. No nodular cell arrangements were seen.

In 21 of 22 parathyroid glands dark chief cells constituted more than 50% of the parenchymal cells, in 16 more than 70% (Fig. 1*a*, *b*). Only in one case there was a dominance of light chief cells and transitional water-clear cells (Fig. 2*a*, *b*). Between 1% and 10% oxyphil and transitional oxyphil cells were observed in 4 glands, in the others these cells were found occasionally.

Cells containing PAS-positive diastase digestible substance (glycogen) were found in all glands. In half the glands 50% to 90% of the parenchymal cells were PAS-positive. In most instances the PAS-reaction was strongly positive.

Argyrophilic cells were found in all 22 glands. In 18 cases the frequency was between 1% and 30% of the total number of parenchymal cells. In the remaining 4 cases argyrophilic cells occurred occasionally. The argyrophilic reaction was weak in most cases and usually located in the cellular periphery. The nuclear diameter was 5.4 μm (S.E. =0.19).

There was no correlation between the different structural features.

Adenomas

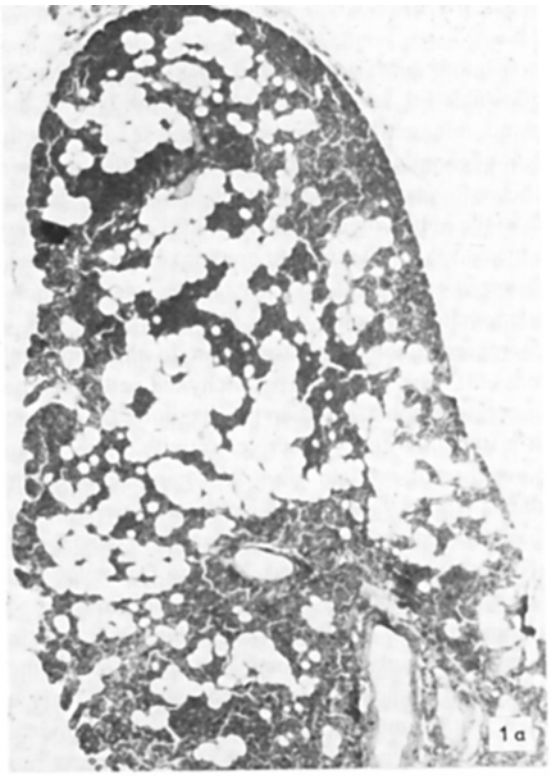
The mean weight of the adenomas was 440 mg with a range from 50 mg to 2 700 mg. In 13 tumours there was a solid arrangement of the parenchymal cells together with some acinar or pseudo-acinar structures. Five adenomas contained two or more noduli surrounded by capsular-like fibrous structures. The remaining cases showed solid parts together with more nodular structures.

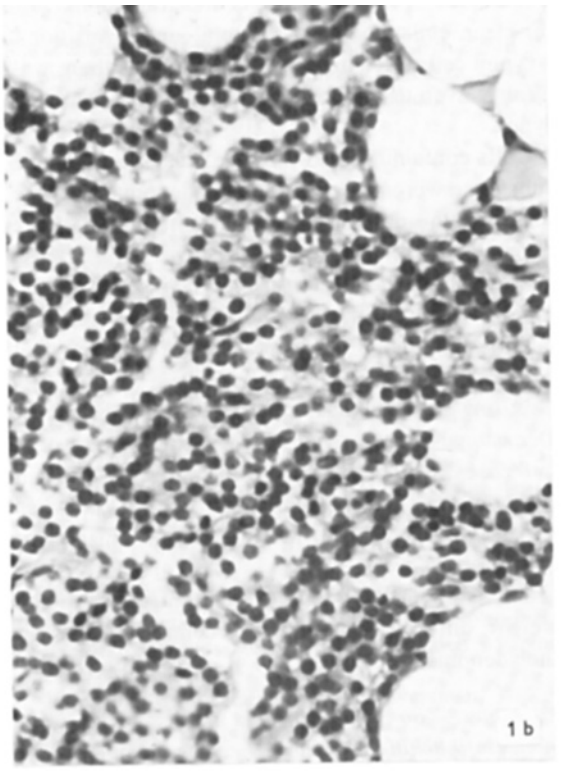
Most adenomas contained small amounts of fat only. In 9 of the tumours a remnant of 'normal' gland tissue was seen outside the connective tissue capsule.

Dark chief cells constituted more than 50% of the parenchymal cells in 13 cases. In 5 there was a

Fig. 1. *(a)* Non-adenomatous parathyroid fat-containing gland, with a predominance of dark chief cells (*b*).

Fig. 2. Non-adenomatous gland with abundant fat (*a*). Light chief cells and transitional water-clear cells predominate. ×32 (1*a*, 2*a*). ×320 (1*b*, 2*b*).


1a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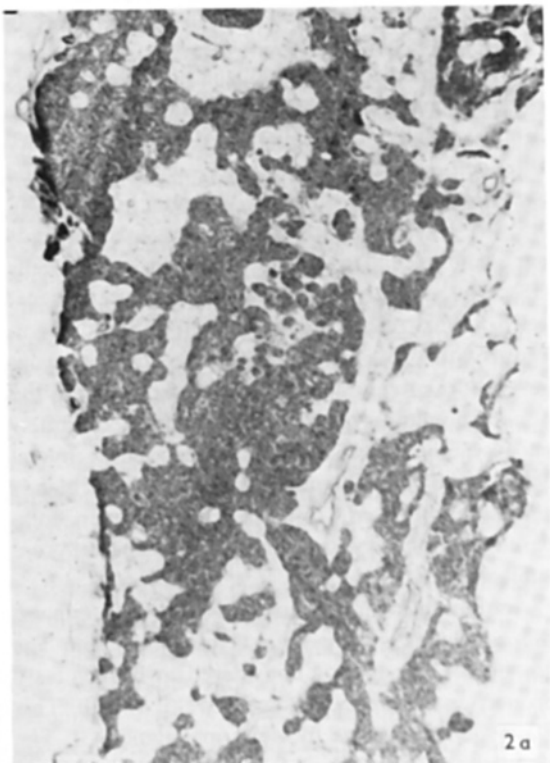
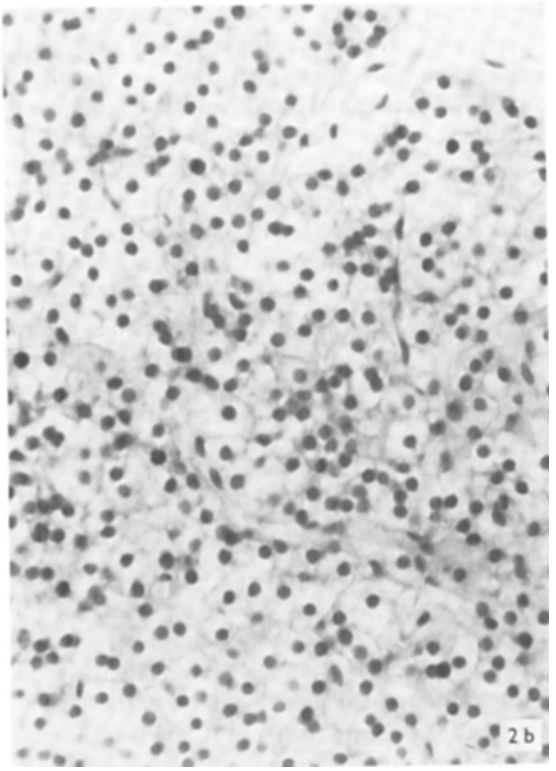

2a


2b

dominance of light chief cells and transitional water-clear cells and in 2 oxyphil and transitional oxyphil cells were in majority. In 2 cases there was a fairly even distribution between the different cell types.

Cells containing PAS-positive diastase-digestible substance were present in every adenoma. In more than half the number of cases the majority of the parenchymal cells were PAS-positive.

Argyrophilic cells were also found in all cases and in about 1/3 of them a positive silver reaction occurred in more than 50% of the parenchymal cells.

In one adenoma several giant nuclei were seen. Occasional large parenchymal cell nuclei were seen in 8 cases. The mean nuclear diameter was 7.0 μm (S.E.=0.48). (The mean diameter was 6.7 μm when the case with marked nuclear polymorphism was excluded.)

There was no obvious correlation between the weight, different structural and cellular features in the adenomas.

Adenoma — non-adenomatous gland interrelationship

Apart from the fact that dark chief cells were predominant in most adenomas as well as in most non-adenomatous glands there was no significant correlation between the weight and the structural properties of the adenoma and the weight and features of the non-adenomatous glands.

The nuclear size in the non-adenomatous parenchyma was smaller than in the adenoma in 19 of 22 cases. The mean difference between the nuclear diameters was 1.6 μm. This difference is highly significant ($p<0.005$). The difference is also significant when the adenoma with several giant nuclei was excluded ($p<0.005$).

DISCUSSION

The mean weight of the non-adenomatous glands in our surgically removed material was 27 mg. In two studies of autopsy material Gilmour & Martin (7) found for 'normal' parathyroid glands a mean value of 30 mg for men and 32 mg for women, and Alveryd (1) reported that 88.5% of 'normal' parathyroid glands weighed between 10 and 49 mg. Thus, the size of the non-adenomatous glands seems fairly normal. Still, it must be kept in mind that we tried to select the largest non-adenomatous gland of each case.

Gilmour & Martin found in adults mean values of glandular fat varying between 38 and 71% of the gland volume depending on age and sex (7). In our non-adenomatous glands about half the number showed a glandular fat content similar to or higher than the above-mentioned values for corresponding age and sex, while the rest contained less fat. Black reported abundant fat in some of the non-adenomatous glands, while in others there was a decreased amount in proportion to the epithelial mass (3). The weight of parenchymal cells must be of greater importance than the glandular fat content in estimating the endocrine activity. The mean parenchymal weight in our non-adenomatous glands was 18.9 mg. This weight is somewhat lower than that reported by Gilmour & Martin, who found a mean value of 20.5 and 22.2 mg for males and females, respectively (7). It seems reasonable to assume that the weight of the parenchymal cells in the remaining glands is somewhat lower than in the extirpated glands, which were selected. Thus a small but no marked decrease in the parenchymal tissue mass seems to occur. No correlation between the size of the adenomas and the extirpated non-adenomatous glands was found.

The histological picture of the non-adenomatous gland was not apparently that of glandular atrophy. In most glands there was a predominance of dark chief cells, which does not agree with an assumed hypofunction, but rather with endocrine activity (15, 19). Even compared with euparathyroid glands our glands seem to contain more dark chief cells (18). The smaller nuclear size of the parenchymal cells in most of the non-adenomatous glands compared with those in the adenoma, however, suggests a relatively lower cellular activity in the non-adenomatous glands. Our findings of differences in nuclear diameter between parenchymal cells in adenomas and non-adenomatous glands agree with those of Cordeiro, who, however, compared adenomas with glands from euparathyroid subjects (5).

Another measure of cellular activity in euparathyroid glands is the cellular glycogen content. The amount of glycogen is considered to be inversely proportional to secretory activity (15, 19, 20). This is, however, not true for abnormal glands (3). The significance of the high glycogen content in our non-adenomatous glands is obscure. It is not clear if

this means a decreased endocrine activity or if these non-adenomatous glands behave in a similar way to the abnormal glands, i.e. where high glycogen content can occur together with high endocrine activity.

The argyrophilic reaction was pronounced in the adenoma in most cases. It is possible that the argyrophilic material represents secretory granulas (11, 15, 19, 22) as is the case in other endocrine cells (4, 10, 12, 21). If such an assumption is correct it would mean that there are more secretory granules in the adenomas than in the non-adenomatous tissue.

If the dark chief cell represents an endocrine active state, as suggested by Roth & Munger (19) and Munger & Roth (15), it seems reasonable to conclude that the non-adenomatous gland in our cases maintained such an activity. The activity is probably somewhat decreased compared to euparathyroid glands (slightly decreased glandular and parenchymal weight) and most of the adenomas (smaller nuclear size in most non-adenomatous glands compared with that in the adenomas). However, even in the presence of large and active adenomas there does not appear to be any histological signs of cellular atrophy in the non-adenomatous glands. Black suggested that there were ultrastructural signs of endocrine inactivity in most of the parathyroid glands resected concomitantly with an adenoma (3). Light-microscopically these glands contained small chief cells but no information is given by Black as to whether they were of the dark or light cell type.

The reason for a maintained activity in non-adenomatous glands is certainly not apparent. One explanation could be that the hormone produced by the adenoma does not completely cover the function of the normal parathyroid production.

The absence of clear signs of atrophy is somewhat surprising. However, it agrees well with the common experience that simple removal of a parathyroid adenoma rarely leads to hypoparathyroidism, even of a transitory nature.

Histologically the non-adenomatous glands did not differ significantly from normal glands (7, 8, 15). This finding is of essential practical importance. In cases where the surgeon suspects a parathyroid adenoma but finds only normal-sized glands the absence or presence of an ectopic adenoma can not be determined by the histological examination of such a gland.

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Address for reprints:

H. Johansson, M. D.
Department of Surgery
University Hospital
S-750 14 Uppsala 14
Sweden