

Incidentalomas and other subclinical abnormalities of endocrine glands in Sri Lankans: An autopsy study

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Abstract

Background:

Incidentalomas of endocrine glands are a common problem in endocrine practice. Data on their prevalence are limited from South Asian settings.

Objective:

We aimed to describe incidentalomas and other histopathological abnormalities in an autopsy series of Sri Lankans.

Methods:

Consecutive autopsies performed at Judicial Medical Office, Colombo from December 2014 to December 2016 were screened and the deceased without a diagnosed endocrinopathy (except diabetes) were included in the study. Pituitary, thyroid, adrenal, pancreas and ovarian specimens were sampled and examined both macroscopically and under light microscopy with Haematoxylin Eosin stain.

Results:

Among 441 autopsies (mean age 52.5 years, male 77.8%) examined, pituitary, thyroid, adrenal, pancreatic and ovarian nodules were detected in 0.8%, 37.2%, 1.8%, 1.3% and 18.4% respectively. Thyroid neoplasms were present in 6.4%, of which 87.5% were papillary carcinoma or papillary microcarcinoma and it was associated with background thyroiditis ($\chi^2 = 4.05$, $p = 0.04$) or nodular thyroid enlargement ($\chi^2 = 32.68$, $p < 0.01$). Thyroiditis was commoner in females, but malignancies showed no gender-predilection. No malignant lesions were identified in pituitary, adrenal, pancreatic or ovarian tissues.

Conclusions:

In this population of Sri Lankan adults, prevalence of thyroid incidentalomas, neoplasms and thyroiditis are comparable to published studies from the West. Papillary carcinoma or microcarcinoma was the commonest type and it showed a predilection to affect thyroid glands with background thyroiditis. Pituitary, pancreatic and adrenal incidentalomas and neoplasms were less prevalent.

Key Words: Prevalence, Pituitary, Thyroid, Adrenal, Pancreas, Ovary, incidentaloma

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Introduction

Incidentally detected tumours and subclinical disease of the endocrine organs have drawn much attention in current practice of endocrinology. Management of such lesions impose a clinical challenge to the physicians as the data on the prevalence, natural history and clinical significance of such lesions on morbidity or mortality are limited.

It is important to establish the prevalence and characteristics of such incidentalomas in the general population as such data may suggest that certain lesions may not progress to clinically significant disease during life. Autopsy series in western countries and India have reported the prevalence of these incidentalomas: pituitary 1.5-31.1% (1-3), adrenal gland 1-32% (3-6) and pancreas (neuroendocrine) up to 10% (7). Although autopsy data are scarce, ovarian incidentalomas are documented as having a prevalence of 3.3-18% on imaging (8). The prevalence of incidentalomas tend to increase with age in all above series. The wide range of prevalence is of note, due to the variation in study population, and techniques used in the autopsy examination.

Thyroid related diseases are a common endocrine disorder, ranging from functional abnormalities to nodular thyroid enlargement. Due to the use of imaging modalities with high sensitivity, many thyroid anomalies are being detected incidentally, posing a challenge on clinical relevance and management strategy, especially in the context of thyroid nodules and papillary microcarcinoma. Autopsy studies on patients in whom clinical thyroid disease were not suspected previously showed a prevalence of nodular goitre 24-26%, follicular adenoma 7-10%, and thyroiditis of 4-9% (9, 10). In similar studies,

papillary microcarcinoma had shown a prevalence of 2-6% (9-14).

As the incidence and prevalence vary according to the population studied and for the fact that such data on incidentalomas and subclinical disease of endocrine organs are not yet available for the Sri Lankan population, we planned to conduct a descriptive autopsy study.

Objective

Aim of the study was to determine the prevalence, evaluate histological characteristics and clinical correlations of incidentally found tumours and other abnormalities of pituitary, thyroid gland, adrenal glands, pancreas and ovaries in autopsy specimen among the study population.

Methods

Study design & Study setting

A cross-sectional descriptive study was conducted on consecutive post-mortem examinations performed at Judicial Medical Office, Institute of Forensic Medicine and Toxicology, Colombo, Sri Lanka from December 2014 to December 2016.

Inclusion & Exclusion criteria

Individuals who had or deceased due to a known endocrine disease or problem except diabetes mellitus, who had previous surgeries on endocrine glands or hormone treatment for endocrine organ related disease, bodies with external signs of putrefaction at the time of the autopsy and bodies with damaged internal organs due to trauma were excluded from the study.

Ethical consideration

Informed written consent was taken from next of kin of each deceased individual. Ethical clearance was obtained from Ethics Review Committee, Faculty of Medicine, University of Colombo.

Data collection, Study instruments & Measurements

A structured interviewer administered questionnaire was used to record demographic and clinical details, administered by a trained interviewer. Information was gathered through medical records and interviewing next of kin of the deceased. Structured format was used to record post-mortem findings, completed by the judicial medical officer conducting the post-mortem. A third form was used to record the findings of pathological evaluation and was completed by the specialist histopathologists performing the examination. In case of discrepancy, consensus was reached by two histopathologists through re-evaluation and final decision was recorded in the database.

Histological evaluation

Specimens of pituitary gland, thyroid gland, adrenal glands, pancreas and ovaries were retrieved after meticulous autopsy and preserved in 10% formalin.

Pathological evaluation was performed by specialist pathologists at Department of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka. Specimens were examined for macroscopic abnormalities. Glands were cut in to thin sections (2mm for pituitary, 3mm for thyroid and ovaries, 5mm for adrenals and pancreas) and examined under light microscope with Haematoxylin Eosin (H&E) stain by two independent specialist pathologists. All macroscopically abnormal regions were examined microscopically. In case of macroscopically normal tissue, entire glandular tissue of pituitary and representative sections of other glands (one each from left and right lobes of thyroid, one each from left and right adrenals, one section each from head, body and tail of pancreas and one each from left and right ovaries) were examined.

Histological diagnoses were based on standard criteria. In thyroid specimens, the diagnosis of papillary carcinoma was made on the presence of papillary carcinoma nuclear features \pm papillary architecture. Papillary carcinomas measuring ≤ 10 mm were designated as papillary microcarcinomas. Encapsulated follicular lesions were designated as follicular neoplasms. Differentiation of follicular carcinoma from adenoma was not made as the number of sections examined from the lesions is limited.

Table 1 : Demographic characteristics of study participants

Parameter	Number
Total population	441
Age (SD) (years)	52.5 (\pm 17.2)
Males (%)	350 (77.8%)
Co - morbidities	
Diabetes (%)	53 (19.1)
Hypertension (%)	80 (22.9)
Ischemic heart disease (%)	48 (13.7)
Family history	
Thyroid malignancy (%)	1 (0.3)
Thyroid disease (%)	8 (2.3)
Ovarian malignancy (%)	2 (0.6)

Statistical analysis

Computer-based data entry was performed on gathered data and was analyzed using SPSS software (Statistical Products and Services Solutions, Chicago, USA) version 20.0.

Results

During the study period of two years, autopsy studies performed on 441 individuals were included in

this analysis. Among those, 77.8% were males and mean age was 52.5 years (SD 17.2). Other clinic-epidemiological information is summarized in Table 1.

Thyroid gland

On macroscopic examination, thyroid gland was normal in 244 (59.9%). Diffuse enlargement, multinodular goiter and solitary nodule were seen in

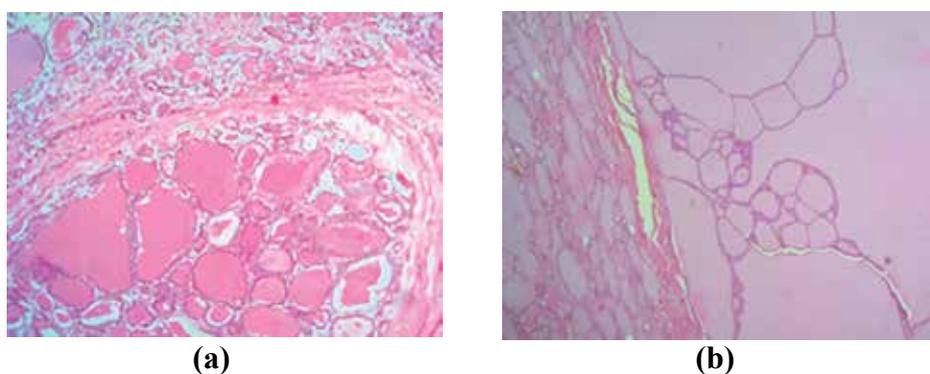


Figure 1: (a) Papillary thyroid carcinoma (x10); (b) Colloid nodule (x 10)

Table 2 : Macroscopic appearance of thyroid gland

	Males (%)	Females (%)	Total (%)
Normal	201 (62.0)	43 (51.8)	244 (59.9)
Diffuse goiter	8 (2.4)	4 (4.8)	12 (2.9)
Multinodular goiter	51 (15.7)	23 (27.7)	74 (18.2)
Solitary nodule	64 (19.7)	13 (15.6)	77 (18.9)

Table 3 : Microscopic features of thyroid gland

Macroscopy	Normal	Colloid	Thyroiditis	Hyperplastic follicles	Papillary carcinoma	Follicular neoplasm	Total
Normal							
Males (%)	157 (81.0)	8 (4.2)	23 (12.1)	1 (0.5)	4 (2.1)	0	193
Females (%)	21 (60)	3 (8.5)	10 (28.6)	0	1 (2.6)	0	35
Total (%)	178 (78.1)	11 (4.8)	33 (14.5)	1 (0.4)	5 (2.2)	0	228
Diffuse goitre							
Males (%)	3 (37.5)	5 (62.5)	0	0	0	0	8
Females (%)	0	0	4 (100.0)	0	0	0	4
Total (%)	3 (25.0)	5 (52.7)	4 (33.3)	0	0	0	12
Multinodular goitre							
Males (%)	2 (3.9)	41 (80.4)	3 (5.9)	0	4 (7.8)	1 (1.9)	51
Females (%)	0	14 (77.8)	4 (22.2)	0	0	0	18
Total (%)	2 (2.9)	55 (79.7)	7 (1.0)	0	4 (5.8)	1 (1.4)	69
Solitary nodule							
Males (%)	12 (21.1)	28 (49.1)	3 (5.2)	2 (3.5)	10 (17.5)	2 (3.5)	57
Females (%)	0	6 (75.0)	0	0	2 (25.0)	0	8
Total (%)	12 (18.5)	34 (52.3)	3 (4.6)	2 (3.1)	12 (18.5)	2 (3.1)	65
Total	195	105	50	3	21	3	377

* Complete data on microscopy were available in 93.4% (228/244) of normal, 100% of diffuse, 93.2% (69/74) of multinodular and 84.4% (65/77) of solitary nodules. Indicated percentages are out of the total number with histology data available.

12 (2.9%), 74 (18.2%) and 77 (18.9%) respectively. Solitary nodules were commoner among males, while diffuse goiter and multinodular goiter were commoner among females (Table 2). Among those with macroscopically normal thyroid glands, histology showed thyroiditis in 14.5% and papillary carcinoma in 2.2%, all of which were papillary microcarcinoma. One third of the diffuse goitres showed thyroiditis while none had neoplastic features. Majority of multinodular goiters were colloid storing while 4 (5.8%) of them had papillary carcinoma (1 of which was a microcarcinoma) and 1 (1.4%)

had a follicular neoplasm. Microscopy of 52.3% of solitary nodules showed colloid nodules, while 12 (18.5%) and 2 (3.1%) showed papillary carcinoma and follicular neoplasms respectively.

Of those papillary carcinomas 5 were microcarcinomas that co-existed with colloid nodules. Overall, 21 (5.5%) thyroid glands harboured papillary carcinomas, of which 10 (47.6%) were microcarcinoma. Prevalence of papillary carcinoma was not significantly different among males and females (5.9% Vs. 4.6%, $p = 0.79$). People with solitary nodules or

multinodular goiters on macroscopic examination were more likely to have papillary carcinoma ($\chi^2 = 32.68$, $p < 0.01$). Background thyroiditis was commoner in specimens with papillary thyroid carcinoma compared to those without, but this association was not statistically significant (Pearson $\chi^2 = 3.23$, $p=0.07$).

Thyroiditis was commoner in females (27.7% Vs 10.6%). One female showed histological features of Hashimoto thyroiditis. Among those with thyroiditis, changes were focal in 16 (32.0%). In people who had thyroiditis, 6 (12.0%) and 1 (2.0%) had papillary and follicular neoplastic foci respectively. All those papillary carcinomas were papillary microcarcinomas.

Among those with colloid goiters, co-existing thyroiditis, papillary carcinoma and follicular neoplasms were seen in 6 (5.7%), 6 (5.7%) and 2 (1.9%) respectively.

Pituitary gland

Three hundred and seventy-three pituitary gland specimens were examined. On macroscopic examination, nodular enlargement of the pituitary was found in three individuals (0.8%), two of which were pituitary adenomas (0.6%). Pituitary calcification and fibrosis were found in the other specimen. One male had an adenoma in macroscopically normal pituitary. Therefore, overall prevalence of pituitary adenoma was 0.8%.

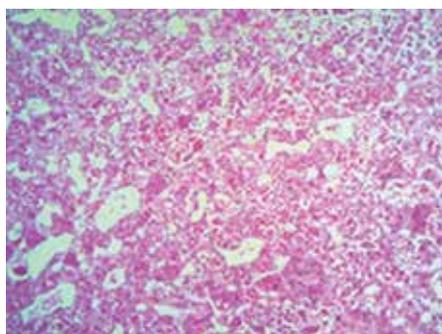


Figure 2 : Pituitary adenoma (x400)

Pancreas

Macroscopically, pancreatic focal lesions were found in six (1.3%) individuals. Two had cystic lesions in the head of pancreas and four had solid lesions equally distributed in head and tail. Their features are summarized in Table 4. Among those with macroscopically normal pancreas, fatty infiltration, fibrosis and benign neoplasms were seen in 40 (10.6%), 14 (3.7%) and one (0.2%) respectively. No malignant lesions were identified in any of the examined specimens. None of these individuals had

extra-pancreatic endocrine organ nodules. Among people with diagnosed diabetes ($n=47$), pancreatic microscopy was normal in majority (76.6%) while fatty infiltration was seen in eight (14.9%) (mild in 6, moderate in 1 and severe in 1) and fibrosis in three (6.4%). Fatty infiltration was commoner in people with diabetes than without (13.1%) but the difference was not statistically significant ($\chi^2 = 0.49$, $p = 0.48$). Similarly, pancreatic fibrosis was also not significantly associated with diabetes ($\chi^2 = 0.008$, $p = 0.92$).

Table 4 Characteristics of pancreatic focal lesions

Patient characteristics*	Macroscopy	Site	Size (mm)**	Microscopy
1 Male, 50 y	Nodular	Head & tail	11 x 9 x 7	Chronic pancreatitis
2 Male, 53 y	Cyst	Head	10 x 8 x 5	Chronic pancreatitis
3 Male, 44 y	Nodular	Head & tail	8 x 9 x 6	Mild fatty infiltration
4 Male, 36 y	Nodular	Head & tail	9 x 7 x 5	Mild fatty infiltration
5 Female, 72 y	Cyst	Head	8 x 5 x 12	Normal pancreatic tissue
6 Female, 25 y	Nodular	Head & tail	10 x 9 x 8	Mild fibrosis

* Patients 2,3 and 4 were alcohol users. None had diabetes

** Where multiple nodules were observed, size of the largest nodule is presented

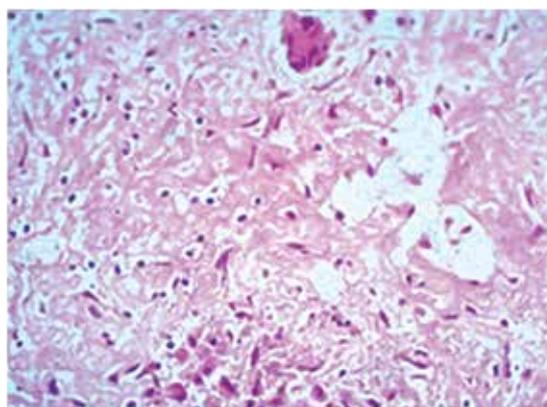
Adrenal glands

On macroscopic examination, diffuse adrenal gland enlargement, nodular enlargement and cysts were observed in 6 (1.6%; 4 bilateral), 7 (1.8%; 1 bilateral), 2 (0.5%; 1 bilateral) respectively. All macroscopic adrenal nodules were measured less than 2cm in diameter.

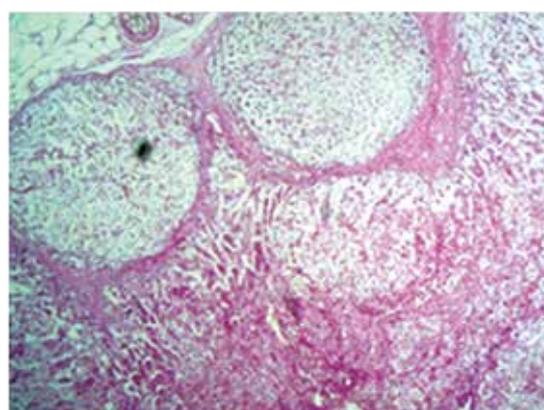
Microscopy of diffusely enlarged adrenal glands were normal in 2, hyperplastic in 3 (all bilateral) and contained caseating granuloma in 1 (bilateral) indi-

vidual. Nodular hyperplasia was seen in 2 individuals (1 bilateral) with macroscopically normal adrenal glands. Unilateral adrenal nodules were commoner on the right gland than the left (5 Vs 2), all being benign.

Among those with nodular enlargement of adrenal, only one showed nodular hyperplasia (which was unilateral) in microscopy while in others it was normal. Microscopy of adrenal cysts was normal. No adenomas or carcinomas were found.



(a)



(b)

Figure 3 : (a) Adrenal granuloma (x400); (b) nodular adrenal hyperplasia (x 40)

Ovaries

From the available number of specimens for ovarian pathology evaluation (n=71), 5 (7.0%) individuals had bilateral multiple ovarian follicular cysts. Unilateral multiple follicular cysts were detected in 6 (8.5%) and 2 (2.8%) in right and left ovaries respectively. One female had bilateral hemorrhagic ovarian cysts. None showed neoplastic features.

Discussion

To the best of our knowledge, this is the first large-scale post-mortem study in Sri Lanka and from a South Asian region investigating the abnormalities of endocrine glands.

Prevalence of pituitary adenoma in this series was 0.8%, lower compared to most other series (15). All of those were microadenomas. Incidence of pituitary adenomas is found to be higher among females and increase with age in other autopsy series (16)[a]. The low rate of pituitary adenomas in our series may be due to lower number of females and relatively young age of the participants in our study. This is because most of our study cohort were recruited from the autopsies done following death after trauma due to road traffic or other accidents

Previously undetected macroscopic thyroid gland abnormalities were detected in 40.1% of the participants, a rate comparable to previous reports (17, 18). Clinically silent occult neoplasms were detected in 6.4% of the participants. Among those with solitary nodules, 21.8% were neoplastic. Majority of those with neoplasms had papillary carcinomas (18 of 21). This is a higher rate compared to other autopsy studies where incidence of occult malignancy ranged between 0.45 – 13% (19, 20).

Higher rates were reported in people from Hiroshima and Nagasaki, in the range of 18.9 – 28.4%. (21, 22). Similar to our observation, most occult neoplasms were papillary carcinomas (23).

Our study also showed an association between chronic thyroiditis and papillary carcinoma. Similar associations have been shown previously between chronic lymphocytic thyroiditis and papillary carcinoma (24, 25).

Prevalence of adrenal nodules were 1.8% in our series, comparable to previous studies reporting 1.45 – 1.97% (26, 27). However, this is much less compared to a similar study from India where 22.4% of specimens had adrenocortical incidental nodules (28). Further, we did not find any neoplasms in histological assessment. In fact, all adrenal nodules were smaller than 2 cm while most malignancies had been observed in adrenal nodules larger than 4 cm (29). Adrenal incidentalomas are relatively rare and the population studied in our series would have been inadequate to capture those rarities. Furthermore, prevalence of adrenal carcinoma increases with age, affecting only 0.2% in young and 6.9% in those 70 years or older (11). Under-representation of older subjects would also have accounted for the lower prevalence of adrenal nodules in this study. In this series, focal lesions of the pancreas were seen in 1.6% of the individuals, a rate lower than previous reports of 6.1% (30). Furthermore, none of the focal lesions showed neoplastic changes in histology. In fact, only one neoplastic lesion was noted in the entire series, which was present in a macroscopically normal pancreas. This is notably different from previous studies where, among focal pancreatic lesions, 31% were malignant and 47% were pre-malignant (30). However, this observation should be interpreted with caution due to the relatively low number of participants included in this series.

Conclusions

In this first large-scale autopsy study on endocrine gland abnormalities in Sri Lankan adults, a lower prevalence of pituitary, adrenal and pancreatic incidentalomas was found compared to previous studies from Western and East Asian countries. However, prevalence of thyroid nodules was comparable to other parts of the world, and most were papillary carcinomas, which showed a predilection to affect thyroid glands with background thyroiditis.

Limitation of the study

There are few limitations in our study. First, special stains or immunohistochemistry studies were not performed due to resource limitations and this limited us from making specific histological diagnoses.

This may also have contributed to low prevalence of incidentalomas since some small lesions may be missed in H&E staining. Second, the clinical data were obtained from next of kin and reviewing medical records, which would have concealed subclinical and undiagnosed diseases. Third, the study was carried out on post mortem examinations performed at a judicial medical centre which introduced a selection bias, recruiting more men and relatively young population, since most post mortems were performed due to unnatural deaths (accidents, violence). An older population would have harboured more incidentalomas in endocrine glands. Fourth, relevant biochemical investigations like thyroid functions, HbA1c, pituitary and adrenal hormone profiles could not be performed which would have yielded more useful information. Furthermore, histological assessment to distinguish follicular adenoma from carcinoma could not be performed since the number of sections examined from lesions were limited.

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Acknowledgement

Not applicable.

Conflict of interest

None.

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