

**EVALUATION OF NUCLEOLAR-ORGANIZER REGION
(NOR) ASSOCIATED PROTEINS IN THE DIAGNOSIS OF
THYROID NEOPLASIA**

Thesis

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BY

Faten Wagdi Ragheb Fahmy

M.B.B.Ch. & M.M.Sc.

Faculty of Medicine-Ain Shams University

Supervised By

Prof. Dr. Adly Farid Ghaly

Prof. of Pathology

Ain Shams University

Prof. Dr. Fawzy Naguib Girgis

Prof. of Pathology

Ain Shams University

Dr. Sanaa A. Sammour

Ass. Prof. of Pathology

Ain Shams University

Dr. Ibrahim M.H. El-Ghazawy

Lecturer of Surgery

Department of surgery

Ain Shams University

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

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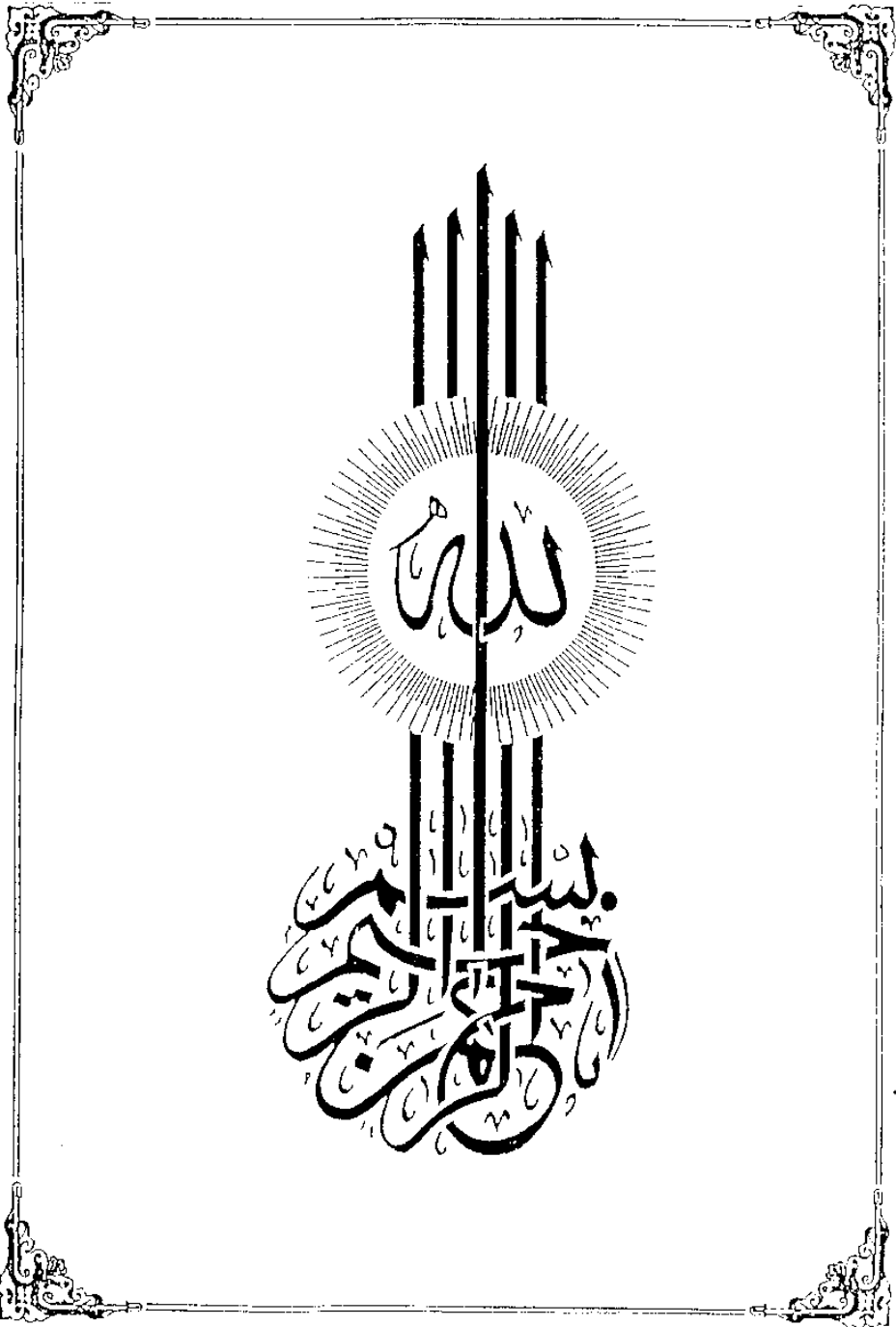
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*INTRODUCTION
AND
AIM OF THE WORK*

Introduction:

In many occasions, thyroid neoplasms may present a real confusing diagnostic problem. Distinguishing follicular adenoma from a hyperplastic nodule, follicular carcinoma and/or atypical adenoma, represent one of wide spectrum of these problems. This difficulty has lead to the search for methods to distinguish these groups of lesions (*Lang et al., 1980*).

Nucleolar organizer regions (NORs), which are loops of DNA encoded for ribosomal RNA production, have been utilized by cytogeneticists for the evaluation of certain genetic disorders (*de La Cruz & Gerald, 1981*). NORs are readily demonstrated by means of the argyrophilia (Ag) of their associated proteins, using the so-called Ag-NOR technique. A recent study showed that this reaction could be applied to routinely processed paraffin tissue sections (*Ploton et al., 1986*).

AgNOR method has been used recently to distinguish between benign and malignant tumours at various sites of body as breast, salivary gland, prostatic neoplasms and melanotic skin lesions, as well as, to assess the grades of malignancy in non-Hodgkin's lymphomas (*Smith & Crocker, 1988*).

Thus, the AgNOR method, which is rapid and simple to apply, offers a new method for the assessment of malignancy at various sites of the body (*Cullimore et al., 1989*).

Aim of the Work:

A retrospective, as well as, a prospective study, of thyroid neoplasia in surgically removed specimens, is to be carried out using AgNOR technique with its correlation to the histopathologic diagnosis, aiming at accurate diagnosis of pure malignant tumours which may be confused with atypical benign lesions by using the routine ways of pathological diagnosis.

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*REVIEW
OF
LITERATURE*

THYROID GLAND

Embryology:

The thyroid gland develops as a tubular evagination from the root of the tongue, called the foramen cecum. It grows downward in front of the trachea and thyroid cartilage. The distal end of this structure proliferates to form the adult gland, while the remainder degenerates and disappears, usually by the fifth to sixth week of development. Persistence of the vestigial tubular structure provides a source for the later development of the thyroglossal cysts. Incomplete descent may lead to a lingual thyroid while excessive descent leads to substernal thyroid glands. Rarely lateral aberrant thyroid nodules develop. Isolated follicles have been identified outside the gland in parathyroid soft tissue in almost 90% of normal adults (*Wilson, 1979*).

Anatomy:

In the adult, the normal thyroid gland weighs 20-25 gm.. Two large lobes are connected in the midline by a broad isthmus from which, on occasion, a pyramidal lobe may protrude superiorly. Occasionally, in a very thin person, this normal pyramidal structure may be mistaken for a thyroid nodule. The close relationship of the recurrent laryngeal nerve and the parathyroid glands makes them extremely vulnerable to injury during thyroid surgery, and also to involvement by spreading malignancy or inflammation (*Hoyes and Kershaw, 1985*).

Histology:

The structural unit of thyroid consists of variably sized follicles that, in three dimensions, compose spheres that are lined by regular cuboidal cells. Ultrastructurally, in addition to the usual cellular organelles, numerous fine microvilli extend from the apical surface of the cells into the follicular colloid, within which is stored by the thyroglobulin. The cells also show secretory granules containing thyroglobulin (*Klinck et al., 1970*).

The cytoplasm of the cuboidal follicular cells has a pale acidophilic staining quality, the greater the activity of the cell, the greater its amount. Follicular cells with abundant granular acidophilic cytoplasm are referred to as Hürthle cells, Askanazy's cells or oxyphilic cells. The intraluminal colloid is pale staining and has scalloped borders in follicles with active secretory function and is densely eosinophilic in inactive ones. In the normal gland, the follicles are separated by a delicate fibrous tissue stroma, which is compacted in some places into fibrous septa that traverse the gland. These septa do not join one another in the substance of the gland, hence the thyroid is not truly lobulated, but pseudolobulated. Thyroid gland is covered by a true capsule of fibroelastic connective tissue sending these fibrous septa. Small collections of lymphocytes are occasionally found in the stroma (*Ham and Cormack, 1979*).

Mitchell et al. (1984) reported that focal collections of lymphocytes were seen at autopsy in the thyroid of about one-half of females and one-

fourth of males, this finding was regarded as a subclinical manifestation of focal lymphocytic thyroiditis.

Dispersed between the follicles are the parafollicular calcitonin-secreting C-cells, which are derived from the neuroectoderm. C-cells in the normal adult are concentrated at the junctions of the upper and middle thirds of the lateral lobes, along the central axes. These cells are extremely difficult to identify in normal gland without the use of immunocytochemical stains for the localization of calcitonin. However, they are more prominent in neonates and in the adults with hypercalcaemia or hypergastrinemia (*Teitelbaum et al., 1971*).

CLASSIFICATION OF THYROID TUMOURS

In thyroid cancer, the histologic picture of the tumour correlates to prognosis and other features in the natural history of the disease better than malignant tumours of most other organs. For these reasons, an accurate histologic classification of thyroid tumours is important (*Franssila, 1971*). With the exception of lymphomas and a few types of rare tumours, malignant neoplasms of thyroid are of glandular epithelial origin. While the classification of carcinomas is not really difficult, it has been complicated by innumerable synonyms and subgroupings (*Woolner, 1971*).

Meissner and Warren (1969) stated that the following classification of thyroid tumours is designed to be helpful not only to the pathological but to the surgeon and clinician as well:

I. Benign:

1. Adenoma:

- Follicular (embryonal, foetal, simple, colloid and oxyphil types).
- Papillary

2. Teratoma:

II. Malignant:

1. Carcinoma:

- Papillary adenocarcinoma
- Follicular carcinoma
 - *Clear cell carcinoma*
 - *Oxyphil carcinoma*
- Medullary carcinoma
- Undifferentiated carcinoma
 - *Small cell carcinoma*
 - *Giant cell carcinoma*
- Epidermoid carcinoma

2. Other malignant tumours:

- Lymphoma
- Sarcoma
- Malignant Teratoma
- Secondary tumour

According to *Hedinger and Sobin (1974)*, the first "*WHO Histological Classification of Thyroid Tumours*" was elaborated by an *International Committee of Thyroid Pathologists working between 1964 and 1972*. It has provided the basis for a number of clinical, pathological and epidemiological studies. They presented the following classification:

I. Epithelial tumours:

A. Benign:

1. Follicular adenoma
2. Others

B. Malignant:

1. Follicular carcinoma
2. Papillary carcinoma
3. Squamous cell carcinoma
4. Undifferentiated carcinoma
 - a. Spindle cell type
 - b. Giant cell type
 - c. Small cell type
5. Medullary carcinoma

II. Non-epithelial tumours:

A. Benign:

B. Malignant:

1. Fibrosarcoma
2. Others

III. Miscellaneous tumours:

1. Carcinosarcoma
2. Malignant haemangioendothelioma
3. Malignant lymphomas
4. Teratomas