MALIGNANT GRANULOMA

THESIS

SUBMITTED FOR PARTIAL FULFILLMENT

OF

THE MASTER OF

OTO - RHINO - LARYNGOLOGY

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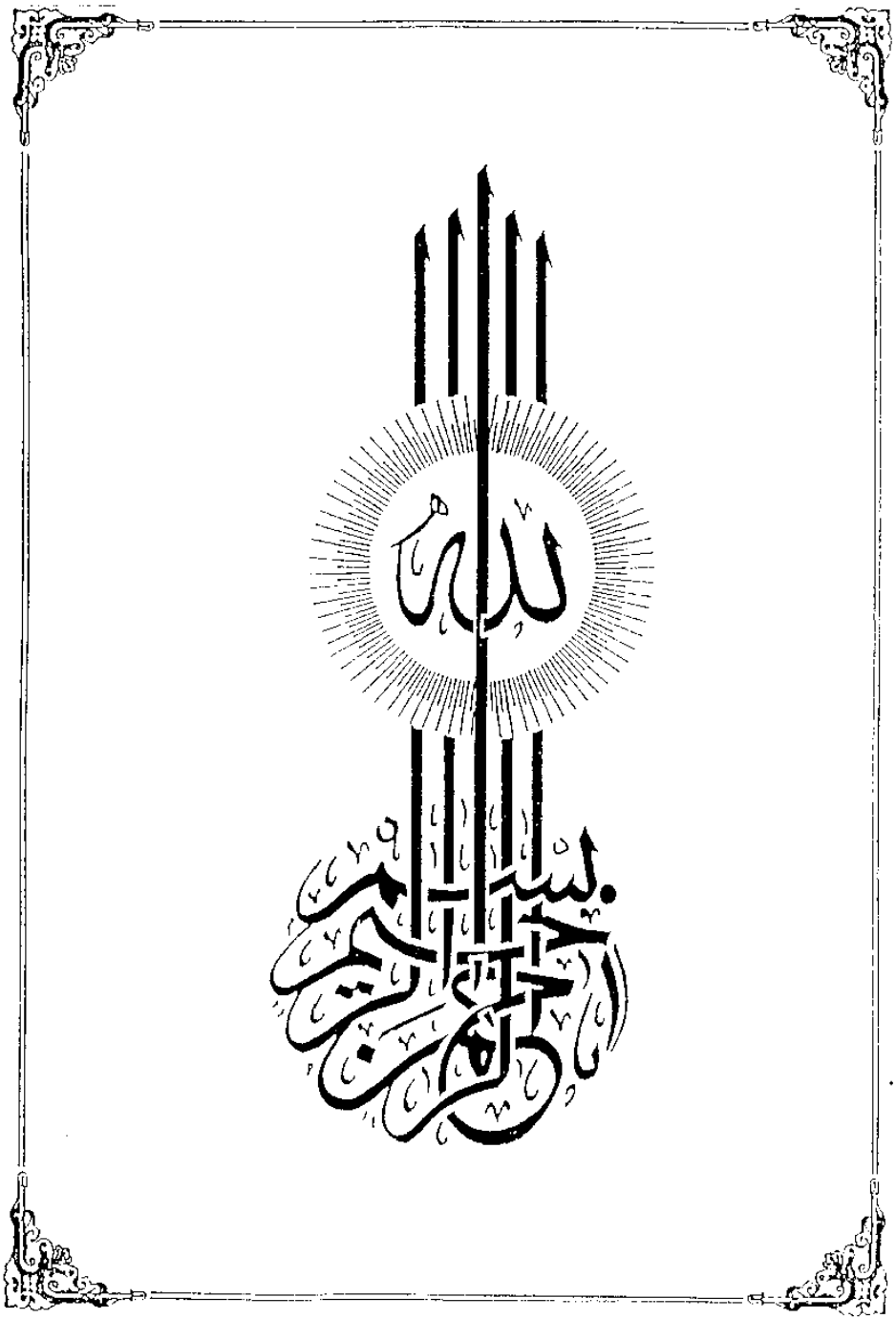
1982

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to Professor Dr. Mohamed Nassar. Professor of Oto-Laryngology, Ain Shams University, for his valuable advice, honest assistance, guidance, kind supervision and continuous encouragement throughout the whole work, without this supervision and support, I would have never been able to write this thesis.

The candidate is indebted to Professor Dr. Amin El-Khodary, Head of Oto-Laryngology Department, Ain Shams University, for his kind approval to register the subject of this thesis. I would like also to thank all the staff members of the Oto-Laryngology Department for their generous encouragement and assistance.



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I. HISTORICAL REVIEW

Definition:

Malignant granuloma is one of many synonyms for a rare clinical syndrome characterised by slowly progressive ulceration and destruction of the nose, paranasal sinuses and occasionaly the pharynx with erosion of soft tissues, cartilage and bone. It may occur as a local lesion or as a part of more generalised condition such as Wegener's granulomatosis.

Historical Review:

Malignant granuloma of the nose has been known to otorhinolaryngologists since its original description in 1897 by McBride, who described the first case with rapid destruction of the nose and face.

Since then opinions of a granuloma affecting this region and occasionly other organs have been the subject of considerable controversy, leading to confusion and uncertainty

about the number of existing varieties of this disease. Thus in addition to 'lethal mid-line granuloma' other descriptive names used are: malignant granuloma, granuloma gangraenescens, mid-line malignant reticulosis, Wegener's granuloma, non healing mid line granuloma, idiopathic mid line granuloma.

The first clear account was published by Robert Woods in 1921 when he aptly described the lesion as a "Wave of granulation tissue advancing irregularly into healthy parts, breaking down behind as it advanced in front, so that there was never any great depth of pathological growth present."

The term "malignant granuloma" was suggested by his colleague Dr. O'Sullivan.

Stewart in 1933 described the condition as a chronic inflommatry process, the accompanying ulceration knowing no limits and destroying the soft parts and the adjoining bones. There was a proliferation of endothelial cells, lymphocytes and plasma cells, and the formation of granulation tissue, at first cellular but later fibrous. In the early stages there was dense small, round cell infilteration with engorged vessels, the blood vessels in established cases

showed enormous thickening of their walls and hyaline change.

Wegener in 1936 and 1939 described cases of necrotizing granulomas of the nose similar to lethal mid-line granuloma, but associated with arteritis and nephritis.

The pathological features of this more wide spread condition were described by Godman and Churg in 1954. They described necrotizing granulomatous lesions affecting either or both the upper and lower respiratory tract with giant cells of both the langhams and foreign body type a frequent feature: A generalised necrotizing vasculitis involving both arteries and viens almost always in the lungs and more or less widely dissemenated in other sites with a necrotizing glomerulitis characterized by necrosis and thrombosis of loops of the capillary tufts. Capsular adhesion and the gradual development of granulomatous lesions in the kidneys.

In 1955 and 1964 Friedmann recommends the use of the term "non-healing granuloma of the nose or non-healing mid-line granuloma". He divides the clinical manifestations into two groups:

1. STEWART'S type, describing the classical pleomorpho cellular histiocytic and usually localised granuloma.

2. Wegener's type, where the principal findings are giant cell granulomas, non-pleomorphic cellular infilterates, necrotizing vasculitis. Presents systemic and nasal manifestations.

He considered both types as "variations of similar underlying pathological condition and as manifestations of a single nosological entity. Cases may, according to Friedmann, be encountered which show features common to both processes, and it is this observation which suggests the close relationship between them.

However Walton in 1959 has recognised both these variations of non-healing granuloma of the face as distinctly separate diseases. He also described a third category of reticulum cell sarcoma which often emerges at an advanced stage in the disease process when the initial biopsies have not been diagnostic, and he mentioned the possibility that such lesions were not intially malignant but were a transformation of a malignant granuloma.

Harrison in 1974 said his opinion, based on personal evaluation of 28 patients with non-healing granuloma or

Wegener's granulomatosis, that where the lesion remains localised to the nose or pharynx, irrespective of the histological appearances, then this condition must be considered as a neoplasm, probably attenuated to a varying degree by the individual's own immunological defences. Occasionly local destruction is slow and limited and the lesion eventually changes into a proved malignant lymphoma.

In 1977 the paper by Michaels and Gregory provides further evidence for the proposal that the Stewart type of non-healing mid-line granuloma is a specific pathological entity,a malignant lymphoma, but of unusual type.

II- ETIOLOGICAL ASPECTS

II. AETIOLOGICAL ASPECTS

The aetiological aspects of lethal mid-line granuloma and Wegener's granulomatosis is obscure. Among the various causes suggested are:

(1) Cassan (1970) reported the intial belief of Wegener's that the dissimenated granuloms were secondary to infarctive necrosis, a belief still held by others. However arteries running into the granulomas are patent, as distinct from those occluded by thrombi proximal to infarcted regions. In addition, the regions diagnosed grossly as infarcts show the typical findings of necrosis and haemorhaege, with a peripheral zone of congestion but without the granulomatous reactions. Vessels near the granulomas, although implicated in the inflammation do not show specific vascular disease.

(2) Shillitoe in 1974, suggested infection among the other causes, the localisation to the upper respiratory tract suggests an infective agent, but no specific micro organisms has been consistently identified in material from

the lesions, tuberculosis, syphilis and fungal infections have all been excluded by numerous negative investigations.

(3) Autoimmunity: This is the most favoured theory of pathogenesis as mentioned by Cassan (1970). An immunologic disorder occuring as a consequence of a single granulomatous reaction to some external, possibly microbial agent that breaks down pulmonary tissue, creating a systemic autoimmune reaction. The beneficial effects of steroids and immunosuppresives such as azathioprine, chlorambucil and nitrogen mustard have been taken as evidence for an immune origin of the disease, but non-specific inflammatory suppression and cyto toxic effects within the lesions have not been excluded. It has been suggested that the respiratory tract is probably the primary locus of attack of the offending agent or the most susceptible sensitized shock tissue. The finding of pulmonary lesions with peribronchial distribution supports the idea that a primary agent gains access in the inspired air. However, the systemic granulomas and vasculitis are enigmatic insofar as they appear to be anatomically unrelated lesions and are both likely to be caused by a hypersenstivity reaction. Although the role

of hypersenstivity in the experimental production both of granuloma and the vasculitis of periarteritis nodosa has been demonstrated in animals, the granulomas have a perivascular distribution, there by differing from both classic and limited Wegener's granulomatosis. G.A. Toma in 1968, reported that the mechanism of auto-immunity is probably based on a delayed hypersenstivity reactions. Whether or not this is due to auto-immune antibodies formed by the cells of the nose or other organ remains to be determined. Toma (1968) suggested that the initial ulcer of the respiratory tract acts as a preparatory or sensitizing dose, and the haematogenous disemination of toxins and/or breakdown products of the hosts altered tissue proteins provide the shocking or challenging dose which results in widespread tissue reaction in the vascular structure of the lungs, kidneys spleen and other organs.

The immunological features of Wegener's granulomatosis and Non-healing mid-line granuloma:

In 1974, Shillitoe and D.F.N. Harrison, have looked for some common markers of autoimmunity, and for immunoglobulin

and cell mediated immune abnormalities, in patients with Wegener's granulomatosis and non-healing mid-line granuloma.

Ten patients were investigated by Harrison, seven of them were diagnosed as having Wegener's granulomatosis and 3 as non-healing mid-line granuloma. The age range of the patients was 31 - 70 years. There was six males and four females.

Auto antibodies in the serum of each patient was investigated. Rheumatoid factor is present in only one patient. Auto antibodies to smooth muscle were noted in four cases.

Serum proteins: protein levels in all but one patient were within the normal range although the albumin levels were generally below and globulin levels above the mean of normal adults.

Immunoglobulins and complement: The level of IgG, IgH, IgM and C_3 in the serum of each patient was determined. It was found that serum levels of IgG were within the normal range, although all but 3 were below the mean concentration of a control population. IgA levels were elevated in all but 2 patients. IgM concentration was increased in four and C_3 concentration in five patients. There was no obvious