GRANULOMATOUS HYPOPHYSITIS
AND THYROIDITIS WITH LYMPHOCYTIC
ADRENALITIS

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"In rare cases the pituitary gland of elderly women may show characteristic granulomas not only with lymphocytic infiltration and epithelioid cells, but also with true giant cells. Independently of the granulomas, giant cells are present also in intact glandular tissue. The granulomas are reminiscent partly of miliary tubercles, but are entirely unrelated to tuberculosis or to syphilis" (Simmonds 1917). Sheehan & Summers, in 1949, collected 18 such cases, including Simmonds' 4, as pituitary "giant-cell granulomas". They concluded that the group may include lesions due to a number of different causes, such as syphilis, tuberculosis, or sarcoidosis, but that in the majority of cases they appear to represent a specific disease process whose aetiology is unknown.

It is our impression from the recent literature that the granulomatous pituitary lesions with giant cells may be divided into 3 groups:

(1) Granulomas due to tuberculosis, syphilis, or sarcoidosis.
(2) Granulomas of unknown aetiology with secondary changes in other organs, especially the thyroid and adrenals as a consequence of pituitary insufficiency—or without such secondary lesions if only a minor part of the hypophysis is involved.
(3) Granulomas of unknown aetiology combined with changes in other organs, especially the thyroid and adrenals, which can hardly be secondary to pituitary insufficiency, int. al. because the histological appearances in these organs are of a type entirely different from that of changes caused by impaired pituitary function.

The object of the present paper is to report and discuss a case of the last-mentioned group.
CASE REPORT

A 74-year-old woman was admitted with the diagnoses: Vertigo, cerebral arteriosclerosis, and arteriosclerotic heart disease.

Ten years previously she had been admitted with concussion and fracture of the cervical spine. No signs of fracture of the skull. During the entire intervening period the patient had been suffering from frequent bouts of dizziness, headache, and tinnitus.

Gynecological history: One normal delivery at the age of 35. Menopause in the 40's.

No tuberculosis in her environment.

Present illness: During the past 6 months the patient had been off colour and sensitive to cold. Three months prior to the present admission influenza-like symptoms simultaneously with others in her environment. Ever since, she had been suffering from bouts of dizziness, increasing headache, tinnitus, and impaired hearing. No tendency to fall, no nausea or vomiting. She also complained of tenderness in all joints, said to have arisen after the influenza. Appetite poor, but she did not know whether she had lost weight. During the past 3-4 weeks she had been in bed. The dizziness had been treated with thiethylperazine maleate (Torecan) and ergotamine tartrate (Bellergetal) tablets, but ineffectively.


Laboratory findings: ESR 35-47 mm/hour. Hb. 74-85 per cent. Red cells 3.16 mill./µl. White cells 2,100-2,200/µl. Differential count: relative lymphocytosis. Platelets: 239,000/µl. Total protein 6.6-7.4 g/100 ml. Paper electrophoresis: 23 per cent γ-globulin (normal 10-18 per cent) and 59 per cent albumin (normal 60-70 per cent). Other fractions within the normal range. Serum electrolytes: Potassium 4.1-3.5 mEq/l., sodium 137-146 mEq/l., chloride 90-97 mEq/l., and total CO2 19-32 mEq/l. Serum calcium 9.3 mg/100 ml, serum phosphorus 4.9 mg/100 ml. PSH 2.1 and 2.3 µg/100 ml T, test 6.1 and 6.9 per cent. Serum cholesterol 204-250 mg/100 ml. Blood sugar 71-89 mg/100 ml. Antistreptococcal haemolysins, agglutination reaction with haemolytic streptococci as antigen, Latex fixation test, anti-human globulin consumption test, anti-nuclear factor. LE cells on three occasions: all negative. Test for cytoplasmic thyroid antibody negative. Antistreptolysin titres: 200 units. ECG: Auricular fibrillation (slow perpetua). Low voltage. Ears and eyes: No abnormalities. EEG: Severe abnormal with runs of 2-3 c/s. activity of increased amplitude, especially bitemporal. Generally reduced dominant frequency.

Owing to the patient's appearance and lethargy, myxoedema soon suggested itself, and the patient was put on thyroid medication, 60 mg daily. However, this had no particular effect upon the clinical condition. One week after the institution of the treatment she developed fever, vomiting, and diarrhea and went into shock. She was treated with fluid, oxygen, digitals (Cedilanid), and terramycin. A sample of faeces sent in for culture of pathogenic intestinal bacteria showed growth of Staph. aureus. The condition rapidly deteriorated, and the patient died within 24 hours. Throughout the stay in hospital she had been hypotensive, having a blood pressure ranging from 70/50 to 120/80 without having been in clinical shock until terminally.

Autopsy: (5730). Slight diffuse enlargement of the thyroid which was of uniform, firm consistency and greyish-red in colour. Adrenals, pancreas, and pituitary grossly normal. No lymph node enlargement. Bronchopneumonic infiltrations in the lower lobes of both lungs. On microscopic examination changes were found in the pituitary, thyroid, and adrenals.

The pituitary (Figs. 1 and 2) showed very severe changes throughout the anterior lobe. There were numerous, medium-sized to large, round or irregular, partly confluent granulomas built up of plump epithelioid cells. Neither the cells nor the granulomas were as well-defined as in
Figs. 1-2.

Fig. 1. Pituitary gland. Ill-defined, confluent epithelioid-cell granulomas. Giant cells of varying size and appearance. Lymphocytic infiltration. × 125. Haematoxylin-eosin.

Fig. 2. Pituitary gland. Vacuolized giant cell with marginal, irregularly distributed nuclei of varying size. × 500. Haematoxylin-eosin.
sarcoidosis. Only a trace of necroses which were non-caseous. Ziehl-Neelsen-stained and Gram-stained sections were negative. No hyalini-
sis, neither peripherally nor inside the granulomas. On the other hand,
pronounced infiltration with lymphocytes in the remaining paren-
chyma and partially also inside the granulomas. Furthermore, in
relation to the granulomas, numerous giant cells of extremely varying
size, far more so than Langhans giant cells. The nuclei were marginal
or irregularly distributed and ranged in number from 20 to almost
100. The cytoplasm was delicately granular, cosinophilic with scattered
coarse vacuoles. No inclusion bodies. Microscopy in polarized light
negative, von Kossa staining for calcium negative. The above-mentioned
changes replaced the greater part of the parenchyma. In sections of
the adrenals the cortex appeared to be slightly narrowed, and the
individual cells were presumably rather smaller than normal, but the
architecture in the various zones was preserved. The medulla was also
preserved, but particularly here there was fairly severe lymphocytic
infiltration in several sites. The infiltrations were almost purely
lymphocytic, apart from occasional plasma cells (Fig. 3). No leuco-
cytes. No hyperaemia or oedema. Serial sections were prepared, but
did not show granulomas, necroses, or giant cells anywhere. Several
sections at different levels of the thyroid gland revealed extremely
severe lymphocytic infiltration. As a rule, the lymphocytes were ar-
ranged in major and minor clusters with germinal centres, lending the
sections an appearance similar to that in Hashimoto's thyroiditis. In
large areas the parenchyma was more or less replaced, and where it
Thyroid gland. Granulomatous area. Vacuolized giant cell. Lymphocytic infiltration. 
× 125. Haematoxylin-eosin.

Thyroid gland. Giant cell with irregularly distributed, partly marginal nuclei of varying size. × 500. Haematoxylin-eosin.

was preserved the follicles were on the whole small with sparse colloid and more or less enlarged epithelial cells with eosinophilic cytoplasm. Here and there granulomas corresponding to those found in the pituitary, both in respect to giant cells and epithelioid-cell granulomas (Figs. 4 and 5).
Case Summary. Autopsy on a 74-year-old woman who had exhibited signs of pluriglandular insufficiency revealed in the pituitary giant-cell granulomas, in the thyroid goitre showing partly granulomas of the same type and partly changes as in Hashimoto's thyroiditis, while the adrenals exhibited lymphocytic infiltration. Histological examination of the lymph nodes, skin, subcutaneous tissue, brain tissue, leptomeninges, myocardium, liver, spleen, and kidneys showed no abnormalities.

DISCUSSION

There is no evidence to indicate that the pathological changes of the pituitary gland were caused by tuberculosis, sarcoidosis, or syphilis. Owing to the localization, the named diseases would be expected to have been generalized. In addition, sarcoidosis involving the pituitary will, in more than 90 per cent, give rise to diabetes insipidus with involvement of the posterior lobe, syphilis usually affects the entire pituitary, and tuberculosis seldom causes hypopituitarism (16). Furthermore, the morphological similarity to the three diseases is fairly modest. In our case the giant cells were of extremely varying size and nucleus, partly with irregularly distributed nuclei and in places with coarsely vacuolated cytoplasm. The epithelioid cells were strikingly plump and the granulomas ill-defined. We found no hyalinosis, fibrosis, caseous necroses, or gumma formation. The histological appearances corresponded accurately to previously described cases of pituitary giant-cell granulomas of unknown aetiology.

Sheehan & Summers (1949) reported two cases of chronic fibrous lesions in the pituitary gland which they interpreted as sequelae to cranial injury, in particular with fracture of the base of the skull. These authors suggested that there might be a question of healed granulomas. Our patient had a history of cranial injury 10 years before her death, but it seems unlikely that this trauma can be related to the active granulomatous process which was entirely devoid of fibrosis.

It is not likely either that the appreciable changes in the adrenals could have been secondary to pituitary insufficiency. True, the patient had reduced function of the anterior pituitary lobe. This is indicated by the clinical findings as well as by the fact that more than three-quarters of the anterior lobe had undergone destruction (21). But apart from doubtful narrowing of the adrenal cortex, there was well-marked lymphocytic infiltration which does not accord with the usual adrenal reaction to hypopituitarism. On the basis of the clinical signs as well as the histological appearances it must be considered likely that the entire disease ran a fairly brief course so that the usual secondary adrenal changes did not have time to develop. It is more difficult to appraise the thyroid changes in relation to pituitary giant-cell granulomas, but they differed in essential respects from the atrophy, fibrosis.
and lymphocytic infiltration often seen secondary to reduced pituitary function. In our case there was mild goitre which presented itself mainly as Hashimoto's thyroiditis, but here and there the thyroid showed changes identical with those found in the pituitary and entirely unlike de Quervain's granulomatous thyroiditis.

It is worth considering whether this case may have represented an extended Schmidt syndrome involving the pituitary. Schmidt, in 1928, described two patients with hypofunction of the adrenals as well as of the pituitary gland. The adrenals showed lymphocytic infiltration and atrophy as in "idiopathic" Addison's disease and the thyroid changes reminiscent of Hashimoto's thyroiditis. Later, Bloodworth et al. (1954) found signs of hypothyroidism in 13 out of 35 patients with primary adrenal insufficiency. Kracht & Hachmeister (1966) interpreted Schmidt's syndrome as the link between auto-immune thyroiditis and those types of primary adenocortical atrophy which have been considered an auto-immune disease. Nerup et al. (1966) found antibody to cytoplasmic antigen in the adrenal cortex of 31 out of 48 patients with "idiopathic" Addison's disease. Of these 31 patients 21 also had thyroid antibodies. Blizzard et al. (1967) demonstrated the same antibody combination in 12 out of 64 patients with adrenal insufficiency. They pointed out that among 57 patients with Hashimoto's disease none had adrenal antibodies and that the incidence of Addison's disease in patients with primary myxœdema is low. Therefore, the autoimmune processes which affect the two glands appear to represent a distinct disease entity, and this is further supported by the fact that the antibodies are organ specific. We have no proof that our case might be a trilaminar Schmidt's syndrome with autoimmune processes directed against all three glands, but below we shall review certain morphological studies which have given rise to reflections in this direction.

Goudie & Pinkerton (1962) suggested the possibility of auto-immunization in a case of hypophysitis and thyroiditis. The thyroid changes were reminiscent of ours, consisting in Hashimoto's thyroiditis with giant cells, but the hypophysis showed severe lymphocytic infiltration without giant cells. The adrenals could not be found. Hume & Roberts (1967) have adduced similar suggestions on the basis of a case of lymphocytic hypophysitis and thyroiditis (without giant cells) combined with adrenal atrophy and pernicious anaemia. Oelbauar & Wainwright (1950) reported a case of typical giant-cell granulomas associated with multiple granulomas of the same type in the adrenals which were, moreover, atrophic. The thyroid exhibited atrophy, fibrosis, and lymphocytic infiltration. These authors did not further discuss the aetiology, but stated that the degree of atrophy in the secondary endocrine organs was not of the advanced type seen following long-lasting hypopituitarism. This was in keeping with the clinical, biochemical, and histological studies which indicated that the pituitary lesion was subacute. About the same applies to our case, only more so.
Doniach & Wright (1951), in one of their two cases of pituitary giant-cell granulomas, found granulomas of exactly the same histological architecture in the adrenals which also showed atrophy. The thyroid exhibited only "adenomata". These authors too did not enter into any aetiological details. Morgenstern (1961) considered the possibility of auto-immunization in a patient with pituitary giant-cell granulomas combined with granulomatous thyroiditis. He also found numerous granulomas in the myocardium and a few in the kidneys and adrenals. Bleisch & Robbins (1952) published 4 cases of giant-cell granulomas. Three were presumably due to sarcoidosis, but this could be ruled out in the fourth case. The adrenals were atrophic, with severe, diffuse lymphocytic infiltration. The thyroid gland was not studied. Subbuswamy et al. (1967) reported one case of pituitary giant-cell granulomas in which the thyroid showed granulomas of the same type. The adrenals were grossly normal, but nothing is stated concerning histological findings. Since the pituitary changes were slight and involved only a small part of the gland, these authors did not interpret the thyroid lesions as being secondary to the pituitary giant-cell granulomas, feeling that the pathological appearances were more likely to be due to a common agent of unknown nature.

All the reported cases of pituitary giant-cell granulomas have had only deficient or no serological studies with a view to autoimmunization. In our case the anti-nuclear factor, anti-human globulin consumption test, and study for cytoplasmic thyroid antibody by immune fluorescence technique were negative. The last-mentioned test is positive in about 90 per cent of sera from patients with diffuse, chronic thyroiditis of the Hashimoto type and in about two-thirds of sera from patients having acquired myxoedema without goitre (Halberg 1967). This would seem to indicate that auto-immune thyroiditis was rather unlikely in our patient. Moreover, Goudie (1968) and Nerup et al. (14) did not find specific pituitary antibodies in patients with idiopathic panhypopituitarism, but it is not known whether these materials included cases of pituitary giant-cell granulomas. There is the possibility that the present technique is not able to demonstrate antibodies in pituitary giant-cell granulomas. Goudie (1962, 1968) feels that the purely lymphocytic type of hypophysitis is presumably of auto-immune nature, and this assumption is supported by experimental investigations (11), while pituitary giant-cell granuloma is perhaps an entirely different disease, and that at present it is not possible to decide its nature. He believes there is a possibility that pituitary giant-cell granuloma is an autoimmune disease in which the morphological signs of the immune reaction differ considerably from that found in most other autoimmune diseases. He goes on: "I should, however, say that granulomata are found in the liver in primary biliary cirrhosis which certainly is associated with non organ-specific autoantibody formation, and I recently encountered at necropsy a
case of "idiopathic" adrenal atrophy in which strong adrenal auto-
antibody was definitely present and in which a single sarcoid-like
follicle was present in the small amount of adrenal cortex which
survived" (7). Our case had granulomatos hypophysitis and thyroid-
ditis, but also thyroid and adrenal changes of the type seen in auto-
immunization. The thyroid and adrenal changes cannot be interpreted
as a consequence of pituitary insufficiency, but all three lesions are
presumably concurrent.

SUMMARY
A case of hypophysitis, thyroiditis, and adrenalitis in a patient with
signs of insufficiency of the anterior pituitary lobe is reported. The
pituitary changes were typical of the granulomatous hypophysitis with
giant cells. The thyroid gland exhibited the same histological appear-
ances and besides lesions like those seen in Hashimoto's thyroiditis. In
the adrenals, lymphocytic infiltration was present. It is considered
likely that the disease has been rather short-lasting and that the
named organic changes are secondary to the same action which is un-
known, but the possibility of auto-immunization is ventilated.

REFERENCES
   of patients with idiopathic adrenal insufficiency (Addison's disease).
3. Bloodworth, J. M. B. et al.: Addison's disease associated with thyroid insuffi-
   ciency and atrophy (Schimdt syndrome). J. Clin. Endocrinol. & Metab. 14:
   540-553, 1954.
4. Doniach, I. & Wright, E. A.: Two cases of giant-cell granuloma of the pituitary
5. Goudie, R. B. & Pinkerton, P. H.: Anterior hypophysitis and Hashimoto's disease
10. Krantz, J. & Hochmeister, U.: Immunopathological aspects in endocrine dis-
11. Levine, S.: Allergic adenohypophysitis: New experimental disease of the pitui-
15. Oelbaum, M. H. & Wainwright, J.: Hypopituitarism in a male due to giant cell
16. Rickards, A. G. & Harvey, P. W.: "Giant-cell granuloma" and the other pituitary


