CLINICAL CONFERENCE

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Myxedema Heart Disease

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THE PATIENT was a 36-year-old housewife at the time of death. She was first admitted to the Toronto General Hospital in 1930, at the age of 14 years, with symptoms and signs of mild hyperthyroidism. At that time her eyes were prominent. Treatment consisted of radium packs to the thyroid area, followed by 10 minims of Lugol's iodine 3 times a day for 1 month. A second course of radium packs was administered 2 months later. Her symptoms abated, only to recur within 6 months. This was usually the sequence of events with radium pack therapy. Following thyroidectomy the patient felt well, and 1 year after her initial admission to hospital it was noted that her eyes were still prominent, but all signs and symptoms of hyperthyroidism had gone.

Early in 1932, because of poor appetite, fatigue, and dry skin, the patient was given desiccated thyroid,* 1/4 gr. per day. By 1935 the dosage had been increased to 1 1/2 gr. per day. During the next 5 years, until 1940, the patient took desiccated thyroid irregularly, at the most 1/2 gr. per day. The basal metabolic rate was done on several occasions during this time and varied from -10 per cent to -40 per cent.

From 1940 to 1946 the patient felt well and had no symptoms of note, although she took thyroid only irregularly. Beginning in 1946, however, she began to tire easily and was short of breath on walking. At this time Dr. M. W. Johnston, who used to see her while shopping, noted that she had the appearance of myxedema. By November 1949 she could not lie flat in bed and said she was "swollen all over." Her salt intake was restricted, and she was given digitalis and mercurial diuretics at home twice weekly. Her edema and orthopnea cleared, but recurred in spite of continued treatment. In May 1950 she was admitted to another hospital and a diagnosis of rheumatic heart disease was made. Treatment consisted of a low-salt diet, digitalis, and Thimerin. The basal metabolic rate was -18 per cent, serum protein 6.6 Gm. per cent, albumin/globulin 4.38/2.28. Urinalysis showed a trace of albumin, the hemoglobin was 93 per cent, and the erythrocyte sedimentation rate was 8 mm. The pulse was 70 to 80 per minute. Her edema cleared once again and she was discharged.

In January 1951, she was admitted to the Toronto General Hospital with the same complaints of swelling of the abdomen, feet, and ankles. These swellings had recurred gradually, despite the fact that she had rested most of the time in bed and had continued on a low-salt diet. At this time the patient had the typical facies, coarse dry skin, and coarse dry hair of hypothyroidism. She also gave a history of intolerance to cold for years. Exophthalmos was still present, with periorbital edema, and there were radiation changes in the skin over the thyroid. There was massive edema to the level of the tenth thoracic spine and ascites. The chest was clear, but the heart was enlarged to the left and right, and showed very little movement under the fluoroscope. There was a questionable mitral presystolic murmur. The blood pressure was 98/80 and the pulse 72 per minute. The electrocardiogram showed low voltage and flat T waves (fig. 1). The basal metabolic rate was -26 per cent. Radioactive iodine uptake was 3 per cent, which is in the hypothyroid range. The serum protein-bound iodine was 1.2 µg. per 100 ml., the serum cholesterol 160 mg. per cent, and the total protein 7.6 Gm. per cent, with an albumin-globulin ratio of 4.8/2.8. During the first week

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* Parke, Davis Company, Canada.
in the hospital therapy consisted of a low-salt diet (1 Gm.), Thiomerin 2 ml. weekly, ammonium chloride, digitalis, and bed rest. Abdominal paracentesis was done and 4.5 L. of fluid were removed. The patient's body weight dropped from 159 lb. to 127 lb. on this regimen. Of this 32-lb. weight loss, the ascitic fluid removed accounted for only 10 lb. At the beginning of her second week in hospital, desiccated thyroid, ½ gr. per day, was given. The symptoms of myxedema subsided, her skin became moist, and her voice changed, but the most remarkable change was in her personality. From a lethargic and apathetic woman, she became quick and alert. After 1 month's treatment with thyroid the supportive therapy was stopped, including digitalis, Thiomerin, ammonium chloride, and low-salt diet. Desiccated thyroid, ½ gr. per day, was continued. Edema recurred, with a gain in weight of 10 lb. Because there had been no reduction in heart size during the month of thyroid therapy, a pericardial tap was done but no fluid was obtained. The supportive therapy was re-established, with subsequent loss of edema. The patient was then discharged, much improved. Gradually the dosage of desiccated thyroid was increased from ½ gr. to 1½ gr. per day. With an increase to 2 gr. a day the patient did not feel well, so the dose was maintained at 1½ gr. An orthodiagram of the heart repeated on April 17, 1951, 3 months after admission to hospital, revealed a transverse diameter of 13.5 cm., compared to the previous measurement of 18 cm. The chest diameter was 23.5 cm. on both occasions (figs. 2 and 3).

In May 1952, the patient was readmitted to the Toronto General Hospital, 5 months pregnant. She said that she had had the best year of her life. She had done all her own housework and was without symptoms, although all treatment had been discontinued with the exception of 1½ gr. of thyroid daily. She had become pregnant and wanted a baby badly. However, she had developed breathlessness rather suddenly one night, and later some edema of the ankles. The serum cholesterol was 138 mg. per cent. The electrocardiogram was normal. She was treated with digitalis, Thiomerin, ferrous sulfate, and 1 gr. of thyroid daily. At this time the transverse diameter of the heart was still 13.5 cm. and the chest 23.1 cm. She was discharged improved and readmitted on July 3, 1952, to deliver spontaneously a 7½-month live baby boy. No signs of cardiac failure were seen at this time. The basal metabolic rate was +13 per cent. She was discharged on July 8, 1952.

She was readmitted on August 7, 1952, because 3 days before she had developed right-sided pleuritic pain with cough and hemoptysis. On admission she was not in discomfort, had some dullness at the right base posteriorly with harsh breath sounds, a friction rub, and occasional rales. The liver was enlarged 1 hand-breadth below the costal margin. Pitting edema of ankles, thighs, and sacrum was present. A diagnosis of pulmonary infarction and congestive heart failure was made.

Treatment consisted of 1-Gm. salt diet, neptal, digitalis leaf, ammonium chloride, and

**Fig. 1.** Electrocardiogram January 1951. Low voltage and flat T waves. Standard leads I, II, and III form the vertical row on the left and precordial leads V5, V4, and V1 the vertical row on the right.
Dicumarol. While on this therapy she began to bleed from the nose and to vomit blood. The prothrombin time was 38 seconds and a simultaneous normal control was 14 seconds. Despite transfusions and vitamin K, she died, 1 month after her final admission. The final diagnoses were myxedema (treated); myxedema heart disease (treated); and pulmonary infarction, repeated.

**AUTOPSY REPORT**

**Gross Examination**

The body was that of a well nourished white woman measuring 5 ft. 5 in. in length and weighing 129 lb. The only external feature of note was moderate edema of the legs, thighs, and sacrum. The right pleural cavity contained 300 ml. of pale fluid; there was none on the left side. The right lung weighed 515 Gm. and had an organizing fibrinous exudate over the lower lobe. Both lower and middle lobes were firm and partially collapsed. The posterior, lateral, and medial basal segments of the lower lobe were involved in a large, wedge-shaped, grey, recent infarct, surrounded by a zone of congestion. The branch of the pulmonary artery to the right lower lobe was occluded by a grey firm embolus. No old infarcts or scars suggestive of previous infarction were seen.

The heart weighed 500 Gm. Both right and left atria were moderately dilated, and both ventricles slightly dilated. The right ventricle measured 0.4 cm. in thickness; the left, 1.4 cm. The endocardium throughout was thin and transparent; all valves and valve cusps appeared normal. The myocardium was also unremarkable, being a uniform red-brown in color. The coronary arteries were normal in caliber and distribution, with a smooth intimal surface free of atheroma. Minimal atheroma only was noted in the aorta.

The liver was enlarged, weighing 2450 Gm., and congested. The spleen was also enlarged, weighing 280 Gm. The kidneys were not remarkable except that in the left kidney there was an old infarct. The uterus was enlarged and soft, its wall measuring 2 cm., in thickness. The intestines contained altered blood, probably originating from the stomach, in which there were many punctate erosions.

The brain was essentially normal and weighed 1250 Gm.

The thyroid gland could not be clearly identified, but lying on the right side of the trachea, just below the thyroid cartilage, was a small oval fragment of greyish firm tissue, weighing 4 Gm.

The adrenal glands together weighed 15 Gm. and were not remarkable.

The pituitary was enlarged and weighed 1.0 Gm.

The remaining organs and systems were not remarkable.

**Microscopic Examination**

The lungs revealed passive congestion and, in the right lower lobe, an infarct in which alveolar structure could be identified, but not any cellular detail. The area of infarction in the kidney appeared considerably older than that in the lung.

The only findings of note in the heart were occasional swollen vacuolated muscle fibers. In some of the vacuoles basophilic mucoid-appearing material could be seen. No areas of fibrosis or other change were noted. Individual muscle fibers were hypertrophied.

The liver sinusoids were markedly distended and stuffed with blood. The liver cells showed fatty metamorphosis, but no necrosis.

The tissue taken to be thyroid consisted of fibrous tissue containing a few acinar-like spaces lined by cuboidal epithelium. They did not contain colloid.

The adrenal cortex and medulla appeared essentially normal.

The pituitary enlargement was apparently due to an increase in chromophobe cells (Mann stain).

**Anatomic Diagnoses.** Myxedema, treated; cardiac hypertrophy with mucoid vacuolation of muscle fibers; infarct of lung; and cardiac failure.
Discussion

The immediate cause of death in this patient was hemorrhage from the stomach, with congestive heart failure as a contributory cause. The finding in the heart of basophilic vacuolation of fibers is not specifically due to myxedema, but may also be encountered in beriberi. A very occasional muscle fiber with similar mucoid vacuolation may be seen in an otherwise normal heart. The histochemical reactions of this material were not too revealing. It gave a positive periodic acid-Schiff reaction and stained with Best's carmine stain.

Nonetheless, it is reasonable to regard this mucoid change as histologic evidence of injury and to relate it to hypothyroidism. Support for this belief is found in the similar accumulations of mucoid material that may occur in skeletal muscle and muscle of the bowel in myxedema, although such accumulations were not found in this case. It is of especial interest that this degenerative change was still evident in the heart at autopsy, although the patient had been receiving desiccated thyroid for some time before death.

Other anatomic changes of myxedema were not encountered. The blood cholesterol was always within a normal range, and atherosclerosis was minimal in the aorta and almost absent in the coronary arteries. The only vascular abnormality was thickening of basement membranes of capillary walls in skin and myocardium. We have noted this change in capillaries in myxedema before, but cannot relate it to therapy. Both treated and untreated cases show it.

Question: Was not the development of myxedema in this patient very slow?

Not unusually so. Apparently the effects of hormone deficiency may be cumulative. In this patient, judging by the basal metabolic rate, hormone deficiency became apparent prior to 1935, and was inadequately treated for the next 5 years. It took another 9 to 10 years before the patient was incapacitated by her disease. This is not unduly remarkable.

Question: What are the criteria for the diagnosis of myxedema heart disease? Is it a common complication of myxedema?

Zondek, who first described the condition in 1918, as a specific entity, laid down the criteria of both right- and left-sided dilatation, usually associated with abnormalities of conduction, and with a definite reduction in transverse diameter of the heart following administration of thyroid gland. These criteria are fulfilled by the present case, in which there was gross cardiac enlargement, to the right and left on x-ray examination, and the electrocardiogram revealed low voltage and flat T waves. There was a reduction of 3.5 cm. in transverse diameter of the heart after 3 months of hormone therapy. It is probable that 70 to 80 per cent of myxedematous patients have some evidence of cardiac involvement, usually in the form of electrocardiographic changes as described, and a slow pulse. Some degree of enlargement is not uncommon in acquired, adult myxedema, but gross involvement, as in the present case, is rare. It is of interest that myxedema heart disease is more common in the middle-aged patient than in the young adult group. In the former, the cause of the enlargement may be coronary sclerosis and its complications.

This brings up the point of relationship of myxedema to coronary sclerosis. In 18 autopsied cases of myxedema in the files of the Toronto General Hospital between 1930 and 1953, coronary sclerosis of moderate to marked degree occurred in 12 cases, but in 9 of these there was in addition essential hypertension. The remaining 6 cases had no hypertension and slight atherosclerosis. Such a series, although small, makes one question the relative importance of hypertension, hypercholesterolemia, and myxedema in the development of coronary sclerosis. The evidence is suggestive that hypertension may be of greater importance in myxedema than any other single factor in enhancing the development of atherosclerosis. In our endocrine clinic, approximately 25 per cent of the cases of myxedema also have hypertension.

Question: What is the pathologic basis of the cardiac enlargement in myxedema?

This is a controversial question, in a sense. Zondek considered the enlargement due to dilatation of all chambers, and remarked on the sluggish action of the cardiac silhouette, “a
lifeless, expressionless mask with deformed contour.” He considered the abnormality one of myocardium. In support of the concept that there is injury to myocardial muscle fibers is the finding of hypertrophy and mucoid vacuolation in them, as in the case under discussion. Edema of the stroma and interstitial tissue may possibly contribute to the enlargement but the tremendous increase in size can only be explained on the basis of dilatation of all chambers, or pericardial effusion, or both. Recently, Kern and his associates have emphasized the importance of pericardial effusion as an early and important factor in the cardiac syndrome of myxedema. Certainly, regression of size of the heart under treatment with thyroid hormone could be just as readily explained by resorption of excess pericardial fluid as it could by shortening of muscle fibers. In the present case there is certainly evidence of injury to the myocardium, still present at autopsy after 18 months’ treatment. The total pathologic change in the heart in the present case is indeed gross, the weight being 500 Gm., and the fibers on microscopic examination showing both hypertrophy and mucoid vacuolation. One could concede the possibility of regression of the mucoid accumulations, but shrinkage of hypertrophied fibers is more difficult to accept.

**Question:** Was this patient’s edema due to congestive failure or to myxedema?

It is difficult to say with certainty. At no time did this patient have jugular venous distention, nor did she ever have rales at lung bases until her terminal illness of pulmonary infarction. And yet, ascites and edema of the lower extremities, extending at one time to the tenth thoracic spine, were present. There were no pleural effusions, and yet the patient was breathless and could not lie flat in bed. This swelling cleared considerably on treatment with digitalis, mercurial diuretics, and salt restriction. It cleared completely following the addition of desiccated thyroid, ½ gr. daily. When, however, the supportive therapy, including the digitalis, mercurials, and salt restriction was withdrawn, edema recurred in spite of continued administration of thyroid hormone. The dose of desiccated thyroid, ½ gr. daily, was small, and duration of treatment short, and it is possible that this may have influenced the response to withdrawal of the drugs. Later, when the dosage of thyroid was increased to 1½ gr. per day and supportive therapy stopped, there was no recurrence of edema. It is also possible that the breathlessness and cardiac enlargement were both due to a pericardial effusion. Against this is the failure to obtain fluid the only time a pericardial tap was attempted. Ascites could have been due to myxedema alone, and the peripheral edema the result of the ascites, and pericardial effusion, compressing systemic venous return. If there were an element of cardiac tamponade from a pericardial effusion, then one might have expected some jugular venous distention. In conclusion, one might say that there is not conclusive evidence one way or the other, of congestive failure in this case. The edema, ascites, and increase in size of the heart shadow, could all be explained on the basis of accumulations of fluid due to myxedema alone. Ellis and his associates consider that there is an element of insufficiency in the cardiac enlargement due to myxedema, and produce fairly convincing evidence to support their thesis.

**Question:** Was replacement therapy adequate in this patient?

From the clinical standpoint, there is no question that until this patient became pregnant, an unusual occurrence in myxedema, therapy appeared adequate. The fact that she became pregnant is good evidence of adequate therapy. Physical signs of myxedema had disappeared, the basal metabolic rate had returned to normal, and the patient stated that she had had the best year of her life. This was on a dosage of 1½ gr. of desiccated thyroid per day, sufficient to raise her protein-bound iodine to normal levels. However, this woman became pregnant, and the level of circulating thyroid hormone increases considerably in pregnancy. From this fact one may deduce that the need for hormone also increases. It is possible then, that she suffered some deficiency during her pregnancy. In support of this is the episode of peripheral edema and breathlessness during the fifth month. Here again, though, explanation of these symptoms is difficult. Were they due to left ventricular strain? The electrocardiogram at this time is reported normal. There
was no change in the orthodiagram, the transverse diameter of the heart remaining at 13.5 cm., and neither basal rales nor jugular venous distention were noted. On looking back, one may suggest that this was the first attack of pulmonary embolism. As the patient suffered only a brief and transient episode of what may be called failure at this time, there would not necessarily be any pathologic sequelae because pulmonary embolism will only produce death of tissue in the presence of congestive failure. At autopsy there were no scars or other changes recognizable as evidence of infarction some 3 months previously.

If these symptoms were due to a recurrence of her myxedema, one might have expected them to increase during the latter part of her course, or persist, as there would not be any appreciable reduction in tissue demand for hormone, and the dose was not increased. However, they did not persist. In further support of the adequacy of therapy from the clinical standpoint is the basal metabolic rate of plus 13 per cent, 1 week before delivery of a normal premature infant. Similarly, if the symptoms were due to heart failure, one might have expected some evidence of insufficiency later on; but none was found until the onset of pulmonary infarction.

The autopsy findings do not resolve the problems in this case; either the question of congestive failure vs. myxedema, or the question of adequate hormone replacement therapy. The tragic terminal complication of pulmonary embolism and infarction did cause an acute cor pulmonale, with peripheral edema and congestion of viscera. The changes in the viscera, however, were those of an acute congestion, with no evidence of earlier chronic passive congestion of either liver or spleen. It was only during this terminal illness that jugular venous distention was noted.

The only evidences of myxedema at autopsy were the changes in the heart and pituitary. Interpretation of these changes is again open to question. One may say that the mucoid change in myocardial fibers is evidence of inadequate hormone therapy; in support of this view are the clinical observations that in myxedema the manifestations vary, not only from one patient to another, but also from one tissue to another in one and the same patient. Hence an amount of hormone sufficient to restore the skin and connective tissues to normal may be inadequate to restore the metabolism of myocardial fibers. Persistent mucoid material in heart muscle may support this hypothesis. On the other hand, there is no proof of the reversibility of the mucoid change in muscle. The increased thickness of capillary walls, as seen in this case, cannot be related to the adequacy of therapy, as pointed out above.

In the pituitary, the increase in number of cells, as evidenced by an increase in weight to 1 Gm., can only be partly explained by the recent pregnancy. Histologic examination revealed an increase in chromophobe cells containing large numbers of small PAS-positive vesicles. This is a common finding in hypothyroidism, especially when replacement therapy has been inadequate. However, in myxedema of long duration before the institution of hormone therapy, some of the pituitary enlargement and cellular increase appears to be irreversible, and this may be the explanation in the case under discussion.10

REFERENCES


