Catecholamine-Induced Myocardial Damage Associated with Phaeochromocytomas and Tetanus

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SUMMARY

Four out of 7 patients dying of phaeochromocytomas and 7 out of 11 dying of tetanus had microscopic widespread myofibre damage (myofibrillar degeneration and myocytolysis). It is suggested that the myocardial lesions in both groups are induced by catecholamine excess.

In those with phaeochromocytomas the excessive catecholamines come from the adrenal tumour, while with tetanus the catecholamines result from tetanus toxin-induced sympathetic nervous system overactivity. Prevention of catecholamine-induced myocardial lesions in both groups may be of importance with regard to prognosis.

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It is well recognised that catecholamines may produce myocardial lesions both in man[1] and in experimental animals.[2,3] Apart from these therapeutic and experimental situations, few reports have been published of diseases in man causing catecholamine-mediated myocardial damage.

Myocardial alterations described in patients with phaeochromocytomas,[4,5] consist of focal areas of myofibrillar degeneration followed by myocytolysis with a non-specific chronic inflammatory cell infiltrate. Northfield[6] reported 3 patients with phaeochromocytomas who died of severe dysrhythmic cardiac complications; 1 had ischaemic necrosis of the left ventricular wall.

Patients undergoing cardiac surgery also have elevated plasma levels of epinephrine and norepinephrine.[7] Patients who died postoperatively had much higher circulating levels of these amines than did survivors.[8] In such patients extracardiac catecholamines could augment those released locally.[9] Unexplained myocardial necrosis[10-12] following cardiac surgery may be related to such catecholamine excess.

MATERIALS AND METHODS

Autopsy material was available for study of 7 patients dying of adrenal phaeochromocytomas, and of 11 other patients who died of tetanus. Tissue sections were stained by the haematoxylin and eosin, periodic acid-Schiff and haematoxylin-basic fuchsin-picric acid methods.

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RESULTS

Patients with Phaeochromocytomas

Four out of the 7 patients dying of phaeochromocytoma had microscopic evidence of widespread myofibre damage (Table I). In only 1 patient (case 4) was the phaeochromocytoma diagnosed antemortem. A few of the myocardial lesions were visible macroscopically in 3 patients. In several instances multiple crops of lesions of varying ages were present in the same heart.

Because of the paucity of reports dealing with myocardial lesions associated with phaeochromocytoma the case histories of 2 of our patients are recorded.

Case Reports

Case 1. A 28-year-old female was admitted to hospital confused and unable to give a history. Physical examination revealed ankle oedema, crepitations over the left lung and hepatomegaly. Her blood pressure was unstable, both hypertensive and hypotensive recordings being obtained on occasions. She was treated with digoxin and diuretics for cardiac failure, and isoprenaline was given occasionally for sudden declines of blood pressure. Her serum alpha-amino transaminase was 121 IU (normal<20 IU). She improved for several days, then suddenly collapsed and died.

At autopsy the right adrenal gland was occupied by a 3-cm diameter phaeochromocytoma. The heart weighed 405 g and all 4 chambers were dilated and hypertrophied. The left ventricle had a large antemortem thrombus adherent to its anterior and septal walls. Both auricular appendages contained antemortem thrombi. The heart valves and coronary arteries were normal. The liver and lungs showed passive congestion. A small thecoma was present in one ovary.

Microscopy confirmed the phaeochromocytoma. Sections of myocardium showed numerous areas of myofibrillar degeneration (Fig. 1) with a scanty lymphocytic infiltrate. No areas of myocytolysis were seen.

TABLE I. DETAILS OF 4 PATIENTS WITH PHAEOCHROMOCYTOMAS AND MYOCARDIAL DAMAGE

Case No.	Sex	Age	Cardiac failure	Heart macroscopic appearance and weight	Histology of myocardium: Myofibrillar degeneration	Myocytolysis	Inflam. cells	Miscellaneous
1	F	28	+	Thrombus in LV 405 g	+	0	Lympho-cytes	Thecoma ovary
2	M	47	+	About a dozen small yellow lesions in LV 624 g	0	Varying ages	Histio-cytes, plasma cells	Infarcts lung, spleen and kidney
3	F	58	+	LV infarct with over-lying thrombus 378 g	0	+ (Well away from infarct)	Lympho-cytes	—
4	M	42	+	LV thrombi and focal lesions 498 g	+	+	Lympho-cytes	Raised urinary VMA

LV = left ventricle; VMA = vanillylmandelic acid.

Fig. 1. Area of myofibrillar degeneration in left ventricle of case 1. The myocardial cells show segmentation and banding of cytoplasm (arrows). **No polymorphs are present (H. and E. × 100).**

Case 2. A male, aged 47 years, had been treated for epilepsy for 3 years and hypertension for 1 year. A week before admission to hospital he complained of dyspnoea, pleuritic chest pain and lumbar pain. Physical examination demonstrated a blood pressure of 150/130 mmHg, left ventricular hypertrophy and bilateral basal crepitations with right-sided bronchial breathing. The clinical diagnosis was hypertensive cardiac failure with lobar pneumonia. A week after admission the patient suddenly collapsed, but was resuscitated; thereafter he had a low urinary output and ventricular premature systoles. Sudden death occurred 2 days later.

At autopsy a phaeochromocytoma was found in the right adrenal gland. Infarcts were present in both lungs, the left kidney and the spleen. The heart weighed 624 g and contained no antemortem thrombi. About a dozen small discrete yellow lesions (the largest 1 cm in diameter) were present in the left ventricle. The coronary arteries showed severe atherosclerosis.

Histology of the myocardium revealed multiple areas of myocytolysis corresponding to the macroscopical lesions. Some lesions appeared recent, whereas in others the myocytolysis was more advanced, and the supporting stroma alone was left and was beginning to collapse. Scanty histiocytes and plasma cells, but no polymorphs, were present (Fig. 2).

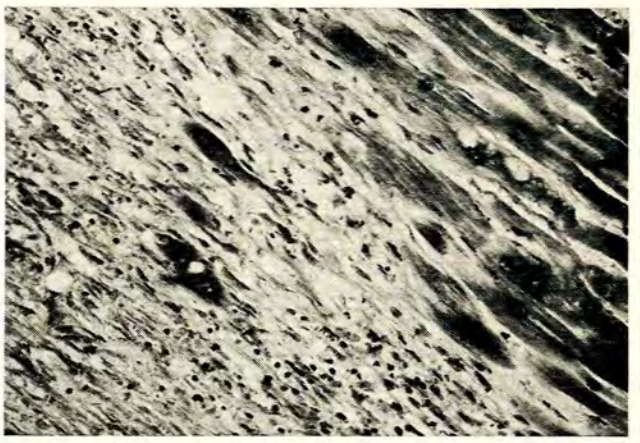

Fig. 2. Case 2. Area of advanced myocytolysis showing a few individual surviving myofibres, collapsed supporting stroma and scanty lymphocytes (H. and E. × 100).

TABLE II. DETAILS OF 7 TETANUS PATIENTS WITH MYOCARDIAL DAMAGE

Case	Sex	Age	Cardiac symptoms and signs	Heart macroscopic appearance and weight	Histology of myocardium		
					Myofibrillar degeneration	Myocytolysis	Inflammatory cells
A	M	40	Evanescent ECG changes of ischaemia; repeated cardiac arrests	Normal 360 g	+	0	Lymphocytes
B	F	52	Fluctuating ECG changes; ? atrial infarct; sudden death	1 cm lesion in LV papillary muscle 320 g	+	+	Lymphocytes; plasma cells
C	F	35	Nil	Normal 220 g	+	0	0
D	M	9	Nil	Normal; no weight	+	0	Lymphocytes
E	M	45	Nil	Normal; no weight	+	0	0
F	M	3/52	Nil	Normal 20 g	0	+	Lymphocytes
G	M	2/52	Nil	Dilated chambers 16 g	0	+	Histiocytes

LV = left ventricle. ECG = electrocardiogram.

Patients with Tetanus

Seven out of the 11 fatal tetanus cases showed microscopic changes in their myocardium — 4 were adults (Table II), one aged 9 years and the others 2 and 3 weeks old. Myofibrillar degeneration (Fig. 3) was present in 5 cases, 3 had multiple areas of myocytolysis, and chronic inflammatory cells were present in 5 hearts. Early collapse fibrosis of the supporting stroma was seen in some of the areas of myocytolysis in case B. Electrocardiographic data were available in the 2 case reports which follow.

Case A. A 40-year-old male presented with a one-day history of trismus, dysphagia and generalised progressive stiffness. No open wound was present, but he had the appearance of a vagabond and had been assaulted a few weeks before admission to hospital.

Examination showed the facies of risus sardonicus, trismus and opisthotonos. His pulse was 94/minute, regular, and the blood pressure 150/90 mmHg. Tetanic spasms were noted. A tracheostomy was performed and he was treated with intermittent positive pressure respiration, skeletal muscle relaxants, sedatives, tetanus antitoxin and antibiotics. Signs of autonomic nervous system overactivity developed with a labile pulse rate and blood pressure. Phenoxybenzamine was given in an attempt to counteract the sympathetic nervous system overactivity.

Fig. 3. Case E, who died of tetanus. Section of myocardium showing myofibrillar degeneration. Cytoplasmic banding is prominent (H. and E. × 100).

Evanescent electrocardiographic changes of ischaemia were present. He was successfully resuscitated after cardiac arrests on two consecutive days, but died of a third cardiac arrest.

Autopsy findings of importance were confined to the heart, which weighed 360 g. The left ventricular free wall

was 15 mm thick and no lesions were seen macroscopically. The coronary arteries were virtually free of atheroma.

Histology demonstrated several areas of myofibrillar degeneration with scanty chronic inflammatory cells in the interstitium.

Case B. A female, aged 52 years, who had been assaulted 3 weeks before hospital admission, but had no open wound, gave a 1-day history of painful spasms of the neck and jaw muscles with difficulty in swallowing and breathing. On examination she had the typical features of tetanus. The pulse was 80/minute and regular. Her blood pressure fluctuated, the diastolic ranging between 70 and 110 mmHg. Culture of a splinter removed from under her right big toe-nail grew coliforms only. A tracheostomy was performed and she was treated with intermittent positive pressure ventilation, skeletal muscle relaxants, tetanus antitoxin and penicillin. Her electrolytes and pO_2 were normal.

The next day she had a cardiac arrest, but resuscitation was successful. The electrocardiogram showed sinus rhythm, rate 120/minute, and P-R interval 0,16 with a normal axis. There was an anterior infarction pattern with left ventricular damage thought to be ischaemic. These changes were present for 4 days and then the electrocardiogram reverted to normal. Estimations of urinary vanillylmandelic acid (VMA) measured an excretion rate of twice normal. The following week serial electrocardiograms fluctuated in appearance as mentioned before, and she then developed florid changes of anterior infarction which persisted until her sudden death of cardiac arrest a week later.

At autopsy the heart weighed 320 g and was pale in appearance. The coronary arteries and heart valves were normal. The only lesion observed macroscopically was a 1-cm diameter area of yellow discoloration in the substance of the posterior-medial papillary muscle. Microscopically the lesion comprised an area of myocytolysis with scanty lymphocytes and early collapse fibrosis. Other smaller areas of myocytolysis were seen elsewhere in the myocardium (Fig. 4).

Fig. 4. Case B, who died of tetanus. Section shows myocytolysis with scanty mononuclear cells and early collapse of the surrounding stroma (H. and E. × 60).

DISCUSSION

Phaeochromocytoma

It is accepted that the catecholamines (epinephrine and norepinephrine) may have deleterious effects on the heart. Catecholamine excess may occur with the therapeutic use of such agents, in patients with phaeochromocytoma and in patients undergoing cardiac surgery. The myocardial changes observed in our cases are the same as those described by other authors.[4,5] The common lesion noted was myofibrillar degeneration, which comprises the development within damaged myofibres of dense, oesinophilic transverse (contraction) bands, alternating with lighter-staining granular zones. While this change may be produced by a variety of influences, it is believed that catecholamines are the final common pathway by which myofibrillar degeneration is induced.[9]

Electron microscopy of myofibrillar degeneration shows that the dense transverse bands are derived from myofilaments which have lost their filamentous structure. Myocytolysis is the next stage. In several of our cases one could find myofibrillar degeneration within myofibres in areas undergoing myocytolysis. Unlike myocardial infarction, a polymorphonuclear leucocyte response was not observed; instead endothelial cells, fibroblasts, histiocytes and scanty lymphocytes and plasma cells were seen in focal aggregates between the vanishing myofibres.

Once phagocytosis of dead myofibres has occurred, a distinctive lesion, comprising a network of reticulin fibres with interstitial cells and histiocytes, is left. Many of the latter contain lipofuscin granules as the tombstones of vanished myofibres. Collapse of the reticulin framework may give the impression of a scar. New fibrous tissue may also be laid down.

The myocardial lesions are said to be usually not visible macroscopically. In 2 of our 4 patients several of the lesions were visible macroscopically. The pallor and slight yellowness of acute lesions may be more evident following formalin fixation.[9] Incubation of myocardial slices in phosphate-buffered nitroblue tetrazolium[18] may aid location of such lesions.

Tetanus

Cardiac involvement in tetanus has received little attention, although occasional reports of electrocardiographic abnormalities in tetanus patients have been published.[14,15] It has been suggested[16,17] that toxic myocarditis may occur in tetanus and may lead to hypotension.

Few pathological details of such cases have been documented. Lassen *et al.*[16] found histological evidence of myocarditis in 1 of their 4 tetanus patients, but the patient also had a septicaemia. Alhady *et al.*[17] had histology of the heart available in only 2 out of 8 fatal tetanus cases. One heart was normal and the other showed interstitial oedema, a scanty mononuclear and plasma cell infiltrate, and necrosis of a few muscle fibres. They interpreted these changes as a toxic myocarditis.

In the German literature Drost *et al.*[18] reported myocardial changes in 16 patients with fatal tetanus. Changes

observed included interstitial oedema, individual cell necrosis and mononuclear cell infiltration. These authors ascribed empirically a direct connexion between tetanus toxin and the heart muscle effect. Murphy [19] reported a case of fatal tetanus with brainstem involvement and myocarditis which he attributed to be direct effects of tetanus toxin. Histologically the myocardium showed necrosis of muscle fibres with an inflammatory cell infiltrate. Overaction of the sympathetic nervous system in severe tetanus has only recently become recognised.[20]

The myocardial changes observed in 7 out of our 11 patients with fatal tetanus correspond closely to those caused by catecholamine excess. Thus myofibrillar degeneration, myocytolysis and chronic inflammatory cells were seen in various combinations (Table II). In none of our patients was there evidence of electrolyte disturbance, anoxia or significant coronary artery atheroma. The specific nature of the myocardial lesions observed in 7 of our cases, together with the clinical signs of sympathetic nervous system over-action, and the excessive urinary vanillylmandelic acid excretion in patient B, leads us to suggest that the myocardial lesions described above may be catecholamine-induced rather than a direct effect on the myocardium of tetanus toxin.

The cardiac-damaging catecholamines in tetanus may be derived from the adrenal medulla or released locally at sympathetic nerve endings within the heart. Experimentally it has been shown that stimulation of a specific area in the mid-brain reticular formation of cats results in a striking sympathetic discharge.[21] Such stimulation will produce cardiac lesions even in adrenalectomised cats, which are indistinguishable from those seen following isoproterenol in rats.

Tetanus toxin may cause comparable sympathetic nervous system stimulation and such sympathetic overactivity has the potential of producing myocardial lesions. It is apparent that the effects of tetanus toxin on the heart are of importance with regard to prognosis. Prevention of catecholamine-induced myocardial lesions in patients with tetanus may be of importance in this regard.

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