SHORT REPORTS

Pleural fluid lysozyme in tuberculous and non-tuberculous pleurisy

In several diseases the concentration of lysozyme is often high in body fluids. Raised serum lysozyme levels have been reported in such granulomatous diseases as sarcoidosis, pulmonary tuberculosis, and Crohn's disease.^{1,2} We have extended studies on the diagnostic significance of lysozyme content in body fluids to the pleural fluid in pleurisy of various aetiologies.

Patients, methods, and results

The series comprised 37 patients admitted to hospital for the diagnostic evaluation of one-sided or bilateral pleurisy. Patients with malignancies of extrapulmonary tissues were not included. The diagnosis of pleurisy was based on clinical, laboratory, and radiological findings. The patients were divided into three groups according to the final diagnosis: (a) those with tuberculous pleurisy, (b) those with non-tuberculous pleurisy (carcinoma, collagenosis, non-specific pleurisy, and pleural effusion of cardiovascular origin), and (c) those with bacterial empyema. Of the 12 tuberculous patients 10 had either a positive culture for *Mycoplasma tuberculosis* or a positive pleural biopsy finding, and in two the diagnosis was based on clinical and radiological findings. With EDTA used as anticoagulant, lysozyme activity was determined simultaneously in plasma and in cell-free pleural fluid with the lysoplate method in which purified human lysozyme was the standard.¹

Lysozyme concentrations in both plasma and pleural fluid were significantly higher in patients with tuberculous pleurisy than in those with non-tuberculous pleurisy (see table). Moreover, the pleural fluid concentration of lysozyme in patients with tuberculosis was significantly higher than the plasma concentration ($P < 0.001$). In 11 out of 12 tuberculous patients but none of the 22 non-tuberculous patients either the concentration of pleural fluid lysozyme was 18.0 mg/l or greater or the pleural fluid:plasma lysozyme ratio was 1.5 or greater. In three patients with bacterial empyema of the pleural cavity lysozyme activity in pleural fluid was raised considerably. In no group of patients did the lysozyme levels in the pleural fluid correlate either with the total number of cells or with the number of non-lymphoid cells in the pleural effusion.

Discussion

The culture of *M. tuberculosis* from pleural fluid has been diagnostic in 20-30% of patients, the culture of pleural biopsy specimens in about 55-80%, and typical histopathological appearances of pleural biopsies in about 60-80% of patients with tuberculous pleurisy.³ Our results, however, show that corroborative additional and specific information for the diagnosis of tuberculous pleurisy can be obtained easily and quickly by the determination of lysozyme in pleural fluid. We do not, however, expect the method we used to distinguish between tuberculous pleurisy and pleural effusions associated with sarcoidosis. Because only 10 μ l of pleural fluid is needed for determining lysozyme activity, this procedure is suitable for studying patients with negligible amounts of pleural effusion.

The origin of lysozyme associated with most inflammatory disorders has been attributed to the accumulation of lysozyme-containing cell types—that is, granulocytes, monocytes, and macrophages—called up by the general inflammatory response. Both in vivo and in vitro the transformation of monocytes into macrophages and epitheloid cells is accompanied by a corresponding increase in the amount of lysosomal enzymes including lysozyme. The microbiocidal power of these cells is progressively increased and mature epitheloid cells have the capacity

to destroy tubercle bacilli. Thus the possible tuberculostatic effect of lysozyme, the co-factor role of lysozyme inhibiting growth of *M. tuberculosis*,⁴ and the observation that phagocytosis is stimulated by human lysozyme⁵ all strongly suggest that the raised concentrations of lysozyme in the vicinity of tuberculous lesions are of pathogenetic importance.

¹ Osserman, E F, and Lawlor, D P, *Journal of Experimental Medicine*, 1966, **124**, 921.

² Perillie, P E, et al, *American Journal of Medical Sciences*, 1973, **265**, 297.

³ Scerbo, J, et al, *Journal of the American Medical Association*, 1971, **218**, 377.

⁴ Thacore, H, and Willett, H P, *Proceedings of the Society of Experimental Biology and Medicine*, 1963, **114**, 43.

⁵ Klockars, M, and Roberts, P, *Acta Haematologica*, 1976, **55**, 289.

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Muscle cramps, collapse, and seizures in two patients taking metolazone

Metolazone is a quinazoline-sulphonamide diuretic used in the treatment of hypertension and oedema. Two patients just starting treatment with the drug developed acute muscle cramps followed by impairment of consciousness and epileptiform movements.

Case reports

A 55-year-old woman had been prescribed metolazone 2.5 mg daily because of a "bloated feeling." She was otherwise healthy and on no other drug. She had been subject to calf-muscle cramps for years. On the third day of treatment she had unusually severe calf-muscle cramps, which recurred suddenly next morning. She collapsed suddenly, remaining unconscious for 10 minutes, during which her husband noted convulsive movements of her left arm and leg. There was no tongue biting or incontinence. She remained drowsy and incoherent for an hour, but physical examination was normal and her blood pressure 120/70 mm Hg. Blood sugar, urea, electrolytes, calcium, cerebrospinal fluid, brain scan, and chest x-ray examination were normal. An electroencephalogram was reported as possibly indicative of epilepsy but not diagnostic. The patient had never lost consciousness before and there was no recurrence after discharge.

A 70-year-old man was referred because of resistant oedema and cor pulmonale. Therapy in the first 14 days consisted of daily theophylline, salbutamol, frusemide 160 mg, and spironolactone 150 mg. Frusemide was then increased to 200 mg daily. Five days later metolazone 5 mg by mouth was prescribed. Twelve hours after this dose he had severe muscle cramps and, minutes later, fell to the ground. Consciousness was impaired, his jaws were tightly clenched, and he was incontinent of urine. The attack lasted two

Mean ($\pm$ SD) lysozyme concentrations (mg/l) in plasma and pleural fluid of patients with tuberculous and non-tuberculous pleurisy

Group	Plasma	Pleural fluid	Pleural fluid:plasma ratio
Tuberculous pleurisy (n = 12)	12.7 $\pm$ 5.0	23.7 $\pm$ 8.7	1.99 $\pm$ 0.7
Non-tuberculous pleurisy (n = 22)	9.3 $\pm$ 3.2	8.3 $\pm$ 3.1	0.89 $\pm$ 0.2
Bacterial empyema (n = 3)	13.5 $\pm$ 3.7	371.6 $\pm$ 47.5	29.0 $\pm$ 9.7

*Student's *t* test.

minutes but cramps persisted for an hour. Examination immediately afterwards was normal with a blood pressure of 120/70 mm Hg. Brain scan, EEG, blood urea, and serum sodium, potassium, and calcium were normal; serum magnesium was low at 0.32 mmol/l (0.78 mg/100 ml). All drugs except metolazone were continued without recurrence of symptoms. The patient recalled an episode of syncope two years previously, when not taking any drug, which lasted for "seconds." This was preceded by a leg cramp but there was no incontinence.

Discussion

These may be cases of serious adverse reaction to metolazone. The features common to both were (1) sudden onset of muscle cramps followed by collapse, impairment of consciousness, and epileptiform movements; (2) no history of epilepsy; (3) each episode closely followed small doses of metolazone; and (4) no further symptoms after withdrawal of metolazone. Gunstone *et al*¹ reported fatal seizures in a patient on metolazone and frusemide. We think this is the only reported association of metolazone therapy and convulsions. Muscle cramps alone, however, are a well-recognised effect of metolazone.^{2 3}

We were unable to find severe hypotension, hypokalaemia, hypocalcaemia, or acid-base disturbances which might have provoked cramps or seizures. In case 2, however, hypomagnesaemia may have been a contributory factor. Hillenbrand and Sherlock³ reported aggravation of hepatic encephalopathy in patients on metolazone, but this seems to have been due to hypokalaemia rather than a direct central nervous system effect. The history of previous leg cramps in both patients is interesting. It suggests enhanced neuromuscular excitation which might be further increased by a direct metolazone effect or by a metolazone-induced electrolyte flux. Pending further investigations to estimate the prevalence of similar reactions to metolazone therapy, we suggest that metolazone should be administered with caution, particularly when there is a history of muscle cramps or epilepsy.

¹ Gunstone, R, *et al*, *Postgraduate Medical Journal*, 1971, **47**, 789.

² Cangiano, J, *et al*, *Current Therapeutic Research*, 1974, **16**, 778.

³ Hillenbrand, P, and Sherlock, S, *British Medical Journal*, 1971, **4**, 266.

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Unusual case of lymphoedema praecox

A case of lymphoedema praecox with some unusual features is reported.

Case report

A 35-year-old nulliparous woman presented with painless swelling of the whole left lower limb of 3 years' duration. She had no other symptoms and no significant or relevant medical or family history. She had not travelled outside Cyprus. She was a small, anaemic woman with obvious left lower limb oedema. The right calf was 33 cm in circumference and the left 44 cm. There were no other abnormal physical signs and no evidence of Turner's syndrome, capillary angiomas, or other congenital anomalies.

Laboratory investigation confirmed a mild iron deficiency anaemia. Marrow biopsy showed hypercellularity but no malignant cells. Blood chemistry, liver function tests, and urine analysis were normal; hydatid complement fixation was negative; and no microfilaria were seen in the blood. X-ray examination of the chest and abdomen, bilateral lower limb venography, and intravenous urography were normal. Bipodal lymphography¹ showed dilated, tortuous lymphatics throughout the left lower limb (fig). There were similar dilated channels in both sides of the pelvis and the para-aortic chains to the level of L2, but the vessels below the level of the superficial inguinal nodes on the right were normal. The oily contrast medium was so slow in

Lymphogram showing grossly dilated lymphatics of left thigh and both sides of pelvis with normal diameter vessels in right thigh.

emptying from the dilated lymphatics that the thoracic duct could not be visualised. The abdominal lymph nodes were normal apart from fibrolipomatous deposits. The normal lymphographic appearances in the lower limb have been described by Browse² and in the lumbar region by Jackson.³

No obstructing lesion in the upper abdomen was found on laparotomy. Lymph nodes excised were histologically normal.

Discussion

Thorough investigation failed to find a cause for the lymphoedema in this case. It may therefore be classified as primary. Primary lymphoedema is arbitrarily divided into (1) congenital; (2) praecox, occurring before age 35; and (3) tarda, starting after 35 years. It may be caused by aplasia, hypoplasia, or hyperplasia of the lymphatics.⁴ In the hypoplastic group decrease in size or number of the lymphatics may be confined to a small area with proximal dilatation. Hyperplastic primary lymphoedema occurs in the absence of an obvious obstructing lesion. It may be unilateral or bilateral. The unilateral type is more common in men with no family history but often with capillary angiomas; the bilateral condition may be familial, more common in women, and associated with a variety of congenital anomalies.

Our case does not fall into either of the recognised clinical groups. Although hyperplastic lymphatics were present unilaterally in the lower limb there were bilateral changes in the abdomen and pelvis. Conventional explanations for the dilated lymphatics in these cases are thoracic duct obstruction or impedance to flow of lymph through the nodes. Competent valves in the vessels of the groin may be protecting the limb from the resistance to flow above that level. As the disease progresses bilateral oedema may develop. In acquired lymphoedema due to lymphadenectomy, radiotherapy, or inflammatory conditions dilated channels are not seen above the level of the lesions. Filariasis may be indicated by a history of visiting an endemic area, the presence of filaria in the blood, and positive filarial skin test.

¹ Dolan, P A, and Moore, A B, *American Journal of Roentgenology*, 1962, **88**, 110.

² Browse, N L, in *The Lymphatics: Diseases, Lymphography and Surgery*, ed J B Kinmonth. London, Edward Arnold, 1972.

³ Jackson, B T, *Annals of the Royal College of Surgeons of England*, 1974, **54**, 3.

⁴ Kinmonth, J B, *The Lymphatics: Diseases, Lymphography and Surgery*. London, Edward Arnold, 1972.

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