Pleuropericardial effusions in children with non-Hodgkin's lymphoma

A report of 2 cases

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Summary

Two children with non-Hodgkin's lymphoma (NHL) who presented with pleuropericardial effusions are reported on. Pericardial effusions are very unusual in children with mediastinal nodal NHL. In the first patient, who presented with a pleural effusion and pericardial tamponade, the diagnosis of NHL was obscured by a false-positive report of acid-fast bacilli in the pleural fluid. The second patient presented with a pleural effusion and a pericardial effusion with superior vena cava obstruction. Rapid filling of the serous cavities was a striking feature in both cases.

Cytological and biochemical investigation of the pleural fluid and pleural biopsy are of limited diagnostic value. Pleuropericardial effusions in NHL are reviewed. The patients have been in disease-free remission for 18 and 16 months respectively.

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Pleuropericardial effusions associated with non-Hodgkin's lymphoma (NHL) are well known in adults and adolescents[1,2] but are unusual in children.[3-5]

NHL with mediastinal nodal disease (MND) at presentation has a natural tendency for rapid dissemination. A minimal delay in confirming the diagnosis is therefore essential.

It is relatively difficult to obtain tissue for histological examination in MND.[5] Pleural aspirates in NHL have a low yield of positive cytological findings,[6-8] specific chemical changes[9] and the findings on pleural or pericardial biopsy are often nonspecific.[10,11] Small pericardial effusions are difficult to diagnose[12] and may rapidly cause cardiac tamponade.[13]

An objective review of the literature is difficult because early reports grouped Hodgkin's disease and NHL together and the differences between NHL in children and adults were not considered.[3]

In this article 2 patients with NHL who presented with pleuropericardial effusions are reported on and pitfalls and problems in establishing the diagnosis are discussed.

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Case reports

Case 1

A 10-year-old boy had been treated for left-sided lobar pneumonia and a pleural effusion with ampicillin, cloxacillin and gentamicin. After a pleural tap, continuous pleural drainage was commenced. Ziehl-Neelsen (Z-N) staining of the pleural fluid demonstrated acid-fast bacilli (AFB), and treatment with isonizid, streptomycin, rifampicin and pyrazinamide was initiated. He was referred to Tygerberg Hospital because he developed progressive dyspnoea and abdominal pain.

The patient was severely dyspnoeic. His temperature was 36°C, the pulse rate 100/min, and the blood pressure 100/70 mmHg; his weight was on the 3rd percentile for age. He had a pulsus paradoxus, elevated jugular venous pressure, an impalpable apex beat, and faintly audible heart sounds. The respiratory rate was 37/min. The trachea was displaced to the right, the left hemithorax stony-dull to percussion, and the liver 5 cm enlarged.

The haemoglobin concentration was 11,1 g/dl, the white cell count (WCC) 17,3 x 10^9/l, (neutrophils 72%, monocytes 6%, lymphocytes 19%, eosinophils 2%, basophils 1%), and the erythrocyte sedimentation rate (ESR) 7 mm/1st h (Westergren). Serum electrolyte and urea levels were within normal limits. Other values were as follows: total serum protein 59 g/l, albumin 30 g/l, total bilirubin 5 μmol/l, asparate aminotransferase 1 164 U/l, alanine aminotransferase 578 U/l, δ-glutamyltransferase 3 U/l, and lactate dehydrogenase (LH) 242 U/l.

A chest radiograph revealed a left-sided pleural effusion, an enlarged globular heart and a distended superior vena cava (Fig. 1). The ECG recorded low-voltage complexes with flattening of ST segments and T waves. Echocardiography demonstrated a massive pericardial effusion and left ventricular decompensation. Pericardial aspiration yielded 200 ml grossly blood-stained fluid with a protein content of 47 g/l, a glucose value of 3,8 mmol/l and

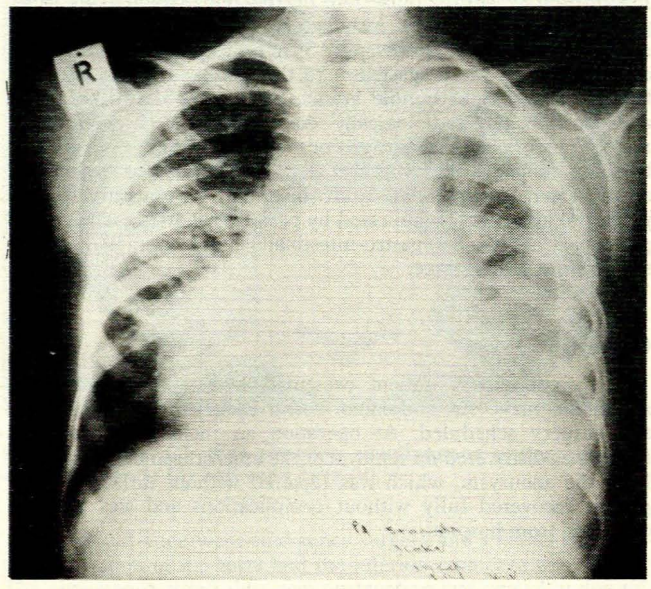

Fig. 1. Case 1. Chest radiograph showing cardiomegaly and pleural effusion.

an LH value of 412 U/l. Culture was sterile and Z-N staining was negative. The pericardial fluid was reported unsuitable for cytological examination.

Pleural aspiration yielded straw-coloured fluid with a protein content of 23 g/l (pleural fluid/serum protein ratio 0,39), a glucose value of 7,5 mmol/l and an LH value of 200 U/l (pleural fluid/serum LH ratio 0,8). Culture was sterile and Z-N staining negative. Degenerating lymphocytes and mesothelial cells were noted on cytological examination. A Mantoux test elicited a 25 mm skin induration. Examination of a gastric aspirate for AFB was negative on three occasions. Ultrasound examination of the abdomen revealed hepatomegaly and distension of the inferior vena cava and hepatic veins. Screening tests for collagen diseases were negative.

Course and management

The dyspnoea improved after a pericardial tap, and treatment was started with isoniazid, ethambutol, streptomycin and prednisone. During the next 2 weeks the signs of pericardial tamponade disappeared and the liver enzyme values returned to normal. The patient was discharged on anti-TB drugs.

The patient again developed progressive dyspnoea, and a chest radiograph confirmed pleural and pericardial effusions. A pericardial tap produced 200 ml bloodstained fluid and a pleural tap 600 ml straw-coloured fluid. He was readmitted 25 days after discharge; 900 ml bloodstained pericardial fluid was removed and numerous mononuclear cells were noted on cytological examination. Three pleural aspirations during the first 5 days after admission yielded 800 ml, 960 ml and 600 ml pleural fluid respectively. A pneumothorax which complicated the last aspiration necessitated insertion of a pleural underwater drain with continuous suction; a further 1 200 ml pleural fluid was drained during the following 18 hours. Analysis of pleural fluid samples showed that the highest pleural fluid/serum protein and LH ratios were 0,52 and 0,48 respectively. The adenosine deaminase (ADA) value was 11,5 U/l. Numerous primitive lymphocytes were reported on cytological examination. Computed tomography demonstrated enlarged mediastinal glands.

Pericardial biopsy revealed tissue infiltration suggestive of lymphoma or leukaemia. A pleural biopsy specimen, bone marrow aspirate and a cerebrospinal fluid sample did not contain malignant cells.

Rapid filling of the serous cavities after each aspiration were noteworthy features of the patient's clinical course. Salt-free albumin was given when the serum albumin value decreased from 37 g/l to 21 g/l. After the start of cyclophosphamide, vincristine, methotrexate and prednisone therapy[14] there was a dramatic decrease in the volume of fluid which drained from the pleural and pericardial cavities, and both drainage tubes could be removed after 6 days. The chest radiograph was normal 40 days later. At the time of writing he had been in disease-free remission for 29 months.

Case 2

A 10-year-old girl was treated for lobar pneumonia and a right-sided pleural effusion. Six weeks later she was readmitted with a temperature of 39°C, cardiac failure and a massive pleural effusion. Pleural aspiration yielded 900 ml fluid and Z-N staining was negative. She was referred to Tygerberg Hospital because of progressive facial oedema and dyspnoea.

The patient's temperature was 36,9°C, the blood pressure 120/60 mmHg and the pulse rate 118/min; her height and weight were on the 3rd percentile for age. She had marked facial oedema. The jugular venous pressure was elevated, the apex beat displaced to the left and a gallop rhythm noted. She had a bulging right hemithorax, left tracheal displacement, dullness to percussion on the right side and 8 cm hepatomegaly.

The haemoglobin concentration was 12,0 g/dl, the WCC 8,52 x 10^9/l (neutrophils 70%, lymphocytes 23%, eosinophils 1%, monocytes 6%), and the platelet count 380 x 10^9/l. The ESR was 38 mm/1st h (Westergren). A chest radiograph revealed a massive right-sided pleural effusion with displacement of the heart and mediastinum to the left (Fig. 2).

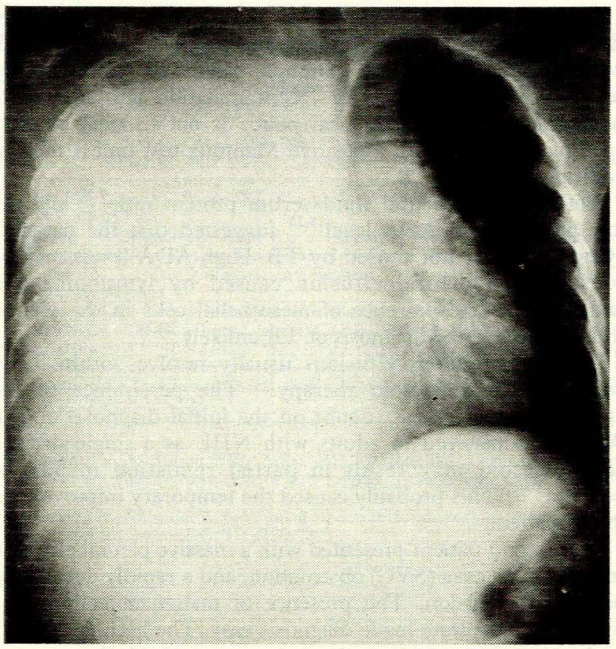

Fig. 2. Case 2. Chest radiograph showing left-sided pleural effusion and mediastinal shift.

The ECG demonstrated low-voltage complexes with depressed ST segments and T waves. Serum electrolyte values were normal and liver function tests negative, except for a raised LH value (609 U/l). The Mantoux test was negative. Pleural aspiration yielded 850 ml bloodstained fluid with a protein content of 49 g/l (pleural fluid/serum protein ratio 0,7), a glucose value of 1,0 mmol/l, an LH value of 294 U/l (pleural fluid/serum LH ratio 4,8) and an ADA value of 278 U/l. No AFB were seen on Z-N staining, and bacterial culture was sterile. On cytological examination cells with an appearance suggestive of small-cell lymphoma were observed. Echocardiography demonstrated a large pericardial effusion. A bone marrow aspirate, a CSF sample and the pleural biopsy specimen did not contain malignant cells. Massively enlarged mediastinal glands due to lymphoblastic lymphoma were found at thoracotomy.

Course and management

Initial therapy consisted of anti-TB drugs, furosemide, digoxin, ampicillin and cloxacillin. The pleural cavity filled up rapidly and a week later clinical signs of a pericardial effusion developed. After thoracotomy the patient developed a pneumothorax and pneumopericardium, and continuous suction drainage tubes were left in both serous cavities. The facial swelling gradually disappeared and both drains could be removed 5 days after the start of chemotherapy with cyclophosphamdide, vincristine, prednisone, daunorubicin, rhioguanine, L-asparaginase, carmustine, cytosine arabinoside and intrathecal methotrexate.[15] The pleural effusion had cleared and the heart had returned to normal size after 18 days. At the time of writing she had been in disease-free remission for 27 months.

Discussion

Pericardial and pleural effusions in tuberculosis

Tuberculosis is the most common notifiable disease in South Africa,[16,17] and pleural effusion is a common finding in patients with pulmonary TB.[16,18] The simultaneous involvement of the pleura and pericardium by TB in children is rare.[16,19]

In our first case incorrect initial management resulted from the positive Mantoux test and the misleading report that AFB were present. The most common causes for false-positive reports are laboratory errors, contamination and inaccurate reporting.[20] The present local policy is not to treat patients aged over 5 years with a positive Mantoux test unless there is additional proof of TB.

Both the low pleural fluid/serum protein ratio[9,21] and the low pleural fluid ADA level[18,22] suggested that the patient's symptoms were not caused by TB. High ADA levels may be present in a pleural effusion caused by lymphoma and leukaemia.[18] The presence of mesothelial cells in the pleural fluid also made the diagnosis of TB unlikely.[23,24]

Large tuberculous effusions usually resolve within 3 - 6 weeks on corticosteroid therapy.[25] The persistence of the effusions therefore cast doubt on the initial diagnosis of TB. When administered to adults with NHL as a single drug, a corticosteroid may result in partial remission in 50% of patients.[26,27] This probably caused the temporary improvement in our patient.

The second patient presented with a massive pleural effusion, superior vena cava (SVC) obstruction, and a rapidly developing pericardial effusion. The presence of malignant cells in the first pleural aspirate made diagnosis easy. The high ADA level in the pleural aspirate was also in keeping with NHL.

Pleural and pericardial effusions in NHL

NHL accounts for 6,5% of all paediatric malignant disease,[28] with the mediastinal nodes being the second most common primary site.[3,29] MND is associated with pleural effusion in up to 58% of children.[4] The most common cause of a pleural effusion is lymphatic obstruction by MND,[8,13] with a resultant transudative or exudative effusion.[8] NHL is also a common cause of SVC obstruction[30] and chylous effusions.[31]

Pericardial effusion may be the presenting sign in NHL.[1,32] If diagnosis is delayed cardiac tamponade may develop rapidly and be aggravated by haemorrhage into the pericardial sac.[1,11,13] MND due to NHL in children tends to spread in a non-contiguous manner,[3] and direct involvement of the pericardium is unusual.[33] Pericardial effusion results from obstruction of cardiac lymph flow by mediastinal nodes.[11,33] The sparsity of lymphatics in the parietal pericardium explains why pericardial biopsy may fail to demonstrate lymphomatous infiltration in the presence of malignant cells in the pericardial fluid.[11,34]

Diagnostic problems

The predominant site of clinically detectable disease in children with NHL is extranodal.[3] Children with MND commonly present with a pleural effusion,[3] less commonly with SVC obstruction,[30] and rarely with a pericardial effusion as in our 2 cases.

Diagnostic procedures on serous fluids have marked limitations. The occurrence of a non-bloody[35] or transudative effusion[8,9] does not exclude malignant disease as a cause. The ADA level may be raised in a patient with a pleural effusion caused by TB or NHL.[18] Positive cytological findings are often the first indication of underlying malignant disease, but cytological examination is diagnostic in only 12,5 - 16% of patients (mostly adults) with lymphoma.[6-8] This is explained by the fact that the pleural effusion may be caused by lymphatic obstruction, pericardial tamponade, SVC obstruction or hypoalbuminaemia.[23] The cytologist may have difficulty in differentiating NHL cells in pleural fluid from reactive lymphocytes or inflammatory cells.[7] The morphological features of lymphomatous cells in the first patient may have been altered by the preceding corticosteroid therapy.[36] Although in this case the bloody pericardial fluid was considered unsuitable for cytological examination, malignant cells have been reported in equal frequencies in bloody and non-bloody serous effusions.[6,35]

Pleural biopsy is often negative in NHL.[10] Pleural infiltration was recorded in 41% of patients with NHL and a pleural effusion at autopsy.[13] Biopsy under direct vision during thoracoscopy will improve the chances of diagnosis.[37]

Numerous cancer markers have been examined in an attempt to clarify the diagnosis of a malignant pleural effusion. Beta-2-microglobulin levels in pleural fluid due to NHL are persistently elevated,[38] and serum levels have been found to correlate with tumour mass and stage.[39]

Echocardiography will confirm a pericardial effusion,[1,12] which is important for correct staging and management. A pericardial biopsy may fail to demonstrate malignant infiltration.[11,34]

Prognosis

In children the presence or absence of a pleural effusion in NHL with MND has no influence on the prognosis.[4] The majority of pericardial effusions in adults with NHL will clear completely within 6 - 8 weeks after the onset of chemotherapy with no adverse effect on prognosis.[1,12] In our patients the drainage tubes could be removed after 6 and 5 days respectively and there was full radiological resolution of the pleural and pericardial effusions after 40 and 18 days respectively.

Conclusion

The early recognition of the malignant nature of a pleural or pericardial effusion secondary to NHL will prevent unnecessary deaths and result in earlier specific therapy. The paediatrician should be aware of the pitfalls and limitations of routine diagnostic procedures in the investigation of serous fluids caused by NHL, especially in areas where TB is endemic. Routine echocardiography should be performed in all patients with MND due to NHL.

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Diaphragmatic paralysis after organophosphate poisoning

A case report

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Summary

Peripheral neuropathy has been described as a rare complication of organophosphate toxicity in man. A case of diaphragmatic paralysis occurring after ingestion of malathion in a suicide attempt is reported. The patient required ventilatory support for 3 months during which time there was slow improvement in the diaphragmatic weakness, which by 6 months had resolved completely.

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Peripheral neuropathy is a well-recognised late complication of acute organophosphate poisoning. Persistent neuropathy resulting from ingestion of commercially available organophosphate insecticides in man is, however, exceptionally rare considering the large number of incidents of acute poisoning.[1-3] This neuropathy is typically both motor and sensory, usually involves peripheral nerves and is commonly permanent. Malathion, a freely available insecticide used extensively in commercial and domestic gardening in South Africa, has been reported as a rare cause of neuropathy.[3,4] A patient who developed diaphragmatic paralysis after acute malathion poisoning is described. This disabling complication of organophosphate poisoning has never previously been documented.

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Case report

A 55-year-old man was admitted to hospital after ingestion of malathion, brodifacoum ('Cooper's Finale') — a vitamin K antagonist — and alcohol in a suicide attempt. Before this he had been well with no history of disease other than a previous history of alcoholism and depression. On admission he was unresponsive and deeply comatose and required intubation and continuous positive pressure ventilation (CPPV) with 5 cm H_2O positive end-expiratory pressure (PEEP). He had clinical evidence of organophosphate poisoning with hyper-salivation, sweating, bradycardia, hypotension, pinpoint pupils, fasciculation and an ileus which later developed into cramping abdominal pain and diarrhoea.

When the patient regained consciousness 24 hours later, his peripheral muscle power was excellent, but his vital capacity (VC) was only 1 100 ml (predicted 4 050 ml). Soon thereafter, however, he developed progressive generalised muscular weakness and he