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.

Pleuropericardial effusions associated with non-Hodgkin's lymphoma (NHL) are well known in adults and adolescents, but are unusual in children. 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. Pleural aspirates in NHL have a low yield of positive cytological findings, specific chemical changes and the findings on pleural or pericardial biopsy are often nonspecific. Small pericardial effusions are difficult to diagnose and may rapidly cause cardiac tamponade. 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.

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.

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 isoniazid, streptomycin, rifampicin and pyrazinamide was initiated. He was referred to Tygerberg Hospital because he developed progressive dyspnoea and abdominal pain.

The patient was severely dysnpeic. 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.

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 flanging of ST segments and T waves. Echocardiography demonstrated a massive pericardial effusion and left ventricular decompensation. Pericardial aspiration yielded 200 ml grossly blood-tainted 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.
Confirmed mono­

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pericardial and pleural 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, metho­

trexate and prednisone therapy was started with isoniazid, ethambutol, streptomycin and predni­
sone. 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.

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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/I). 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

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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 disease-free remission for 29 months.

The chest radiograph was normal 40 days later. At the time of writing he had been in disease-free remission for 29 months.

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 10^3/l (neutrophils 70%, lymphocytes 23%, eosinophils 3%, mono­
cytes 6%), and the platelet count 380 x 10^3/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).

Discussion

Pericardial and pleural effusions in tuberculosis

Tuberculosis is the most common notifiable disease in South Africa, and pleural effusion is a common finding in patients with pulmonary TB. The simultaneous involvement of the pleura and pericardium by TB in children is rare.
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. 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 and the
low pleural fluid ADA level 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. The presence of mesothelial cells in the pleural
fluid also made the diagnosis of TB unlikely.

Large tuberculous effusions usually resolve within 3 - 6
weeks on corticosteroid therapy. 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. This probably caused the temporary improvement
in the 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, with
the mediastinal nodes being the second most common
primary site. MND is associated with pleural effusion in up
to 58% of children. The most common cause of a pleural
effusion is lymphatic obstruction by MND, with a resultant
transudative or exudative effusion. NHL is also a common
cause of SVC obstruction and chylos effusions.

Pericardial effusion may be the presenting sign in NHL. If
diagnosis is delayed cardiac tamponade may develop rapidly
and be aggravated by haemorrhage into the pericardial sac.
MND due to NHL in children tends to spread in a non-con-
tiguous manner, and direct involvement of the pericardium is
unusual.

Pericardial effusion results from obstruction of
cardiac lymph flow by mediastinal nodes. 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.

Diagnostic problems

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

Diagnostic procedures on serous fluids have marked limita-
tions. The occurrence of a non-bloody or transudative effu-
sion 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. 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. This is explained
by the fact that the pleural effusion may be caused by lymphatic
obstruction, pericardial tamponade, SVC obstruction or hypo-
albuminaemia. The cytologist may have difficulty in differenti-
ating NHL cells in pleural fluid from reactive lymphocytes
or inflammatory cells. The morphological features of lympho-
matous cells in the first patient may have been altered by the
preceeding corticosteroid therapy. Although in this case the
bloody pericardial fluid was considered unsuitable for cyto-
logical examination, malignant cells have been reported in
equal frequencies in bloody and non-bloody serous effusions.

Pleural biopsy is often negative in NHL. Pleural infiltra-
tion was recorded in 41% of patients with NHL and a pleural
effusion at autopsy. Biopsy under direct vision during
thoracoscopy will improve the chances of diagnosis.

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 persist-
tently elevated, and serum levels have been found to correlate
with tumour mass and stage.

Echocardiography will confirm a pericardial effusion, which
is important for correct staging and management. A
pericardial biopsy may fail to demonstrate malignant infiltra-

Prognosis

In children the presence or absence of a pleural effusion
in NHL with MND has no influence on the prognosis. 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.

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
Peripher al 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.

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. 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. A patient who developed diaphragmatic paralysis after acute malathion poisoning is described. This disabling complication of organophosphate poisoning has never previously been documented.

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 with pinpoint pupils, fasciculation and an ileus which later developed into cramping abdominal pain and diarrhoea.

When the patient regained consciousness 24 hours later, his blood pressure (PEEP) was only 1100 mmHg (predicted 4050 mmHg). Soon thereafter, however, he developed progressive generalised muscular weakness and he was only able to sit up with assistance.

Peripheral neuropathy has been described as a rare cause of neuropathy. A patient who developed diaphragmatic paralysis after acute malathion poisoning is described. This disabling complication of organophosphate poisoning has never previously been documented.