LYMPHANGIOLEIOMYOMATOSIS WITH CHYLOUS ASCITES

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ABSTRACT

A 41-year-old Malay housewife presented with recurrent chylous ascites and progressive cachexia over 17 years. A diagnosis of lymphangioleiomyomatosis (LAM) was established by laparotomy where biopsy of the liver, peritoneum and adhesions from previous surgery showed smooth muscle proliferation in the blood vessels and lymphatics. Clinically and radiologically, there was no evidence of pulmonary involvement. She was treated with dietary fat restriction and medium-chain triglycerides. This is the first case of LAM reported in Malaysia.

Keywords: *lymphangioleiomyomatosis, chylous ascites, steroid receptors, hormonal manipulation, medium-chain triglycerides.*

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INTRODUCTION

LAM is a rare disease which is exclusive to women of child-bearing age[1,2]. It was first described by Cornog and Enterline in 1966[3] and the 101st and 102nd cases were reported as recently as 1987[4].

The disease is characterised by a benign proliferation of smooth muscle cells lining the lymphatic vessels in the abdomen and chest[5]. Chest involvement, manifesting as recurrent pneumothoraces, chylous effusions and a chronic obstructive lung disease with or without abdominal involvement is by far commoner than the latter alone[6].

Patients with pulmonary LAM rarely survive more than 10 years from the time of diagnosis[1,7] but patients with pure abdominal involvement have been known to survive much longer[1,8].

Treatment has been largely symptomatic and palliative in the past but in the last 5 years it has been aimed at achieving long-term remission with hormonal manipulation and cytotoxic chemotherapy.

We present here a rare case of LAM presenting with a protracted history of recurrent chylous ascites but without pulmonary involvement.

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CASE REPORT

A 41-year-old Malay housewife was admitted with recurrent ascites and progressive cachexia. At the age of 24 years, she developed ascites and abdominal pain 8 days after delivering her first child. Although the reasons were not clear from her records, an exploratory laparotomy was performed. This revealed "dirty-looking" fluid. She was lost to follow-up but returned at the age of 29 years to deliver her second and last child. Over the next 6 years, she developed progressive ascites and weight loss and was seen by a gynaecologist after a provisional but erroneous diagnosis of ovarian carcinoma was made elsewhere. She was empirically started on antituberculous chemotherapy for provisional diagnosis of peritoneal tuberculosis(TB). Unfortunately, after 2 months of treatment, she was again lost to follow-up.

She claimed to have remained well until the present admission. During this admission, "pink milky" ascitic fluid was drained from her peritoneal cavity. Cultures of this fluid showed secondary infection with *E. Coli* and appropriate antibiotics were administered parenterally. She was then referred to the Gastroenterology Unit for advice.

She gave no history of vomiting, upper gastrointestinal bleeding, alteration in bowel habits or rectal bleeding to suggest a gastrointestinal malignancy. Although her father, with whom she had been living had pulmonary TB, the patient herself did not have a cough, hemoptysis, fevers, or sweats to suggest active TB. She had not lived in or travelled to areas known to be endemic for filariasis. She did however complain of increasing lethargy, postural dizziness and effort intolerance.

Her menses were normal. She denied having used any form of contraception in the past. She did not smoke or drink alcohol.

Examination revealed a cachexic woman with a pulse of 80 per minutes, blood pressure 110/70 mmHg, respirations 20 per minutes and temperature 37.5°C. There was no finger clubbing and no stigmata of chronic liver disease. There was no significant lymphadenopathy. She was clinically anaemic. Examination of her heart and lungs was normal. There was gross ascites and no abdominal masses were palpable. Neurological examination was normal.

Her haemoglobin was 9.5 g/l, white cell count 10,600/mm^3 (neutrophils 69%, lymphocytes 19%, monocytes 10%, eosinophils 2%) and platelets 1,232,000/mm^3. The blood film showed dimorphism of the red blood cells.

Her random blood glucose was 5.1 mmol/l. Blood urea was 4.0 mmol, sodium 126 mmol, potassium 3.0 mmol and creatinine 80 umol per litre. Total protein was 65 (normal range NR:60-85) g/l, albumin 24 (NR:26-52) g/l, bilirubin 10 (NR:3-21) umol/l, alkaline phosphatase 96 (NR:30-115) units

and alanine transaminase 28 (NR:0-40) units per litre. Serum calcium was 2.14 (NR:2.13-2.63) and phosphate 1.56 (NR:0.81-1.45) mmol/l. Her erythrocyte sedimentation rate was 70 mm in one hour. Arterial blood gas analysis showed a pH of 7.53, bicarbonate 27.2 (NR:22-26) mmol/l, and the following partial pressures: oxygen 13.5 (NR:10.7-13.3) kPa and carbon dioxide 4.3 (NR:4.07-4.6) kPa. Serum cholesterol was 3.8 mmol, triglyceride 2.7 mmol, LDL-cholesterol 2.3 mmol and HDL-cholesterol 0.3 mmol per litre. Her alpha-fetoprotein was negative. Serum prolactin was 319 (NR:117-468) mU, mid-luteal progesterone less than 1.8 mmol, human choriogonadotrophic hormone less than 8 (NR<12) IU, testosterone 0.4 (NR:0.9-2.8) nmol, thyroxine 73 (NR:70-167) nmol and triiodothyronine less than 0.8 (NR:1.3-2.6) nmol per litre. Chest X-ray was normal.

Abdominal paracentesis revealed thick milky fluid containing 460 red blood cells and 20 lymphocytes. The fluid was sterile and a Ziehl-Neelsen stain and cultures for acid-fast bacilli were negative. Blood examination for microfilaria (*Brugia malayi* and *Wuchereria bancrofti*) was negative. Her xylose absorption test was normal.

Endoscopic and radiologic examinations of the upper and lower gastrointestinal tracts were normal. Abdominal and pelvic ultrasound showed marked ascites with a bulky uterus suspended in fluid and at least 3 cysts in an enlarged right ovary. The left ovary was normal. The liver and kidneys appeared normal.

At laparotomy, 8 litres of chylous peritoneal fluid was drained. There were multiple adhesions from previous surgery. The liver was normal but "felt cirrhotic on cutting". The uterus was bulky and contained several fibroids. The stomach, small and large bowel, fallopian tubes and ovaries appeared normal. Examination of the chylous fluid was again not helpful and was negative for acid-fast bacilli. A wedge biopsy of the liver, peritoneal tissue and adhesions were sent for histopathological examination.

Sections from the peritoneum showed a prominent network of dilated vascular and lymphatic spaces lined by endothelium. Some of these showed pinkish granular material whilst others were either empty or contained blood. Orientated around many of these spaces were slender, irregular bundles of smooth muscle cells against a background of fibrous tissue. Scattered foci of lymphoid aggregates, plasma cells and areas of haemorrhage and acute inflammation with neutrophils were also present. The sectioned adhesions also showed similar changes. The surface of the liver showed similar dilated lymphatic spaces with associated smooth muscle proliferation. The liver parenchyma showed several irregular angioma-like lesions lined by endothelium containing erythrocytes. The portal tracts also contained similar dilated vascular spaces. These findings were consistent with a diagnosis of LAM. Lymphangiography was refused by the patient.

Treatment was initially symptomatic. She was prescribed a low fat diet which was supplemented with medium-chain triglycerides.

Parenteral nutrition consisting of essential amino acids, intralipid, dextrose and vitamins was later instituted. Although she gained 3 kg in body weight, her post operative course was complicated by intra-abdominal sepsis and severe depression. She discharged herself against advice on the 45th post-operative day.

DISCUSSION

LAM was first described by Cornog and Enterline[3] in 1966. It is said to be a disease exclusive to women of child-bearing age[1]. Because of this, it is thought to be hormone-dependent and modified by various factors. In particular, oestrogens[9] and pregnancy[5] have been reported to aggravate LAM. This is reflected in the present case in which ascites had accumulated shortly after both pregnancies. More recently however, LAM has been reported in males[10-12] and children[13,14] as well. Pathologically, it is characterised by a benign proliferation of smooth muscle in the muscle lining of the abdominal and thoracic lymphatics, veins and bronchioles[15,16]. Some authors believe that it is a hamartomatous proliferation[3,17], while others claim that it is a forme fruste of the tuberous sclerosis complex[18,19].

Approximately 1% of patients with tuberous sclerosis also have pulmonary LAM[8]. It is histologically indistinguishable from "primary" LAM. Our patient however showed none of the other protean manifestations of tuberous sclerosis and lacked a positive family history. In many of the case reports, including ours, there were coexistent uterine myomata[10,20], an occurrence more frequent than can be accounted for by chance. It is postulated that oestrogen plays a role in the stimulation of smooth muscle in both the lung and uterus[1].

Various forms of symptomatic treatment have been used with variable success. These include dietary fat restriction and medium-chain triglycerides[21], peritoneal-jugular shunts[22], closed tube thoracostomy, pleurectomy, chest tubes with sclerosing agents and thoracic duct ligation[23]. Although curative treatment using irradiation[7,24] and cyclophosphamide[23] has been used in the past, more recent trials have been with hormonal manipulation.

Steroid receptors for oestrogen and progesterone have been identified in tissue affected by LAM[25-29]. Since then there has been a proliferation of reports in the literature on the use of oophorectomy, progesterone and tamoxifen in various combinations for the treatment of LAM[1,30-36]. Owing to the rarity of this disease, most of these reports have been anecdotal and interpretation of the efficacy of various treatments has been difficult. In their review of 32 patients with LAM, Taylor et al[37] found that treatment with medroxyprogesterone acetate had the most beneficial effect on the course of the disease. They also observed that oophorectomy alone did not influence progression of the disease and recommended that it only be used as a second line of therapy. Poh and Wang[30] calculated a 26% success rate with progesterone treatment if they included cases from Taylor et al as well as their cases. However, opinion about the efficacy of oophorectomy is not uniform. Another evaluation of a large series of 30 cases of LAM treated with eight regimens of hormonal treatment revealed that the administration of progesterone or oophorectomy or both are the most effective treatment resulting in improvement or stabilisation of the disease in the majority of cases[34]. More recently, successful treatment with an analogue of luteinizing hormone-releasing hormone (LHRH) has been reported[38,39]. Zahner et al[24] also reported one case with LAM who responded to a combination of radiotherapy and hormonal castration with the LHRH antagonist, goserelin.

Although it has generally been held that survival beyond 10 years from the onset of disease is rare, 75% of the patients from the series of Taylor et al[37] were still living $8\frac{1}{2}$ years after the onset of disease. They concluded that the rate of progression of LAM can vary widely among patients and that it was not clear from their review whether the improved survival was due to hormonal manipulation.

We suggest that in a patient of child-bearing age with recurrent chylous ascites, in whom commoner causes such as tuberculosis, filariasis (in endemic areas), chronic liver disease and lymphoma[40] have been excluded, a diligent search for lymphangioleiomyomatosis must be made. And, if diagnosed, the patient should receive a trial of a low fat diet and

medium-chain triglycerides and progesterone and/or oophorectomy.

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