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CASE REPORT

Extrapulmonary lymphangioleiomyomatosis: an unusual cause of biliary tract obstruction

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ABSTRACT

We present a patient who was diagnosed with retroperitoneal lymphangioleiomyomatosis (LAM) and who developed biliary tract obstruction caused by LAM in the papilla of Vater. After endoscopic retrograde cholangiopancreatography (ERCP) and papillotomy, the patient's liver enzymes normalised. Disease progression was slowed down with gosereline and interferon alpha 2b (IFN-α2b). In patients with LAM and signs of biliary tract obstruction, disseminated LAM should be considered. IFN-α2b can be a useful treatment in patients with widespread LAM.

KEYWORDS

Biliary tract obstruction, extrapulmonary, lymphangioleiomyomatosis

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is characterised by non-neoplastic proliferation of abnormal smooth muscle cells (LAM cells) that almost exclusively affects women in their reproductive years. LAM is a rare systemic disease and the main manifestations are pulmonary.[1,2] Although LAM can occur in subjects with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous syndrome, most patients have sporadic LAM.[1]

Due to the rarity of this disease, many clinicians are unfamiliar with LAM. Hence, clinical management represents a great challenge, occasionally resulting in a delayed or missed diagnosis, unnecessary operative intervention, and inappropriate therapy. We report a case of a woman who was initially diagnosed with retroperitoneal LAM and subsequently developed pulmonary LAM in combination with elevated liver enzymes. This is the first case describing LAM of the papilla of Vater and it provides novel insights into the treatment of this rare disease.

CASE REPORT

This 23-year-old, otherwise healthy, woman presented with progressive abdominal pain. There was no significant family history. She did not have dyspnoea or chest discomfort. On physical examination no abnormalities were found and haematological tests were normal. On transvaginal ultrasonography, the ovaries were normal. A computed tomography (CT) scan of the abdomen showed a large retroperitoneal mass, 13 x 7 x 16 cm, with cystic and solid components in the lower right abdomen which extended around the abdominal aorta and inferior vena cava. A high resolution (HR) CT scan of the thorax was normal. Upon laparotomy, the mass was irresectable. Histology was highly characteristic of LAM and showed proliferation of smooth muscle tissue surrounding dilated lymph and blood vessels. These smooth muscle cells contained monomorphic oval nuclei with blunt-ended nuclei. Immunohistochemistry was positive for actin but negative for desmin. These findings are highly characteristic of LAM.

She started on a gonadoreline (GnRH) agonist (gosereline) 3.6 mg monthly and tamoxifen 40 mg daily. However, because of disease progression the tamoxifen was stopped and replaced by monthly medroxyprogesterone 500 mg in combination with thalidomide 50 mg daily (which has antiangiogenic and immunomodulating effects). Nevertheless, the disease progressed and HRCT of the thorax one year after diagnosis demonstrated pulmonary LAM. Subsequently, the medroxyprogesterone and thalidomide were stopped. Based on a case report describing

successful treatment of LAM with systemically applied interferon alpha 2b (IFN-α2b)[3] she was started on IFN-α2b 3 x 10^6 U three times a week. Abdominal and thoracic CT scans showed stable disease. However, liver enzymes became elevated (reference values are given in parenthesis): alkaline phosphatase (ALP) 111 U/l (<100), gamma-glutamyl transferase (γGT) 183 U/l (<25), aspartate aminotransferase (AST) 29 U/l (<30), alanine aminotransferase (ALT) 37 U/l (<30) and bilirubin 5 μmol/l (<5). This was attributed to the IFN-α2b but since the liver enzymes were only mildly elevated, treatment was continued. In the course of seven years, follow-up abdominal and thoracic CT scans showed stable disease under IFN-α2b but the liver enzymes kept increasing (ALP 215 U/l, γGT 520 U/l, AST 28 U/l, ALT 39 U/l, and bilirubin 10 μmol/l after seven years). Eventually, an abdominal CT scan showed dilated bile ducts without evidence of bile stones. On endoscopic retrograde cholangiopancreatography (ERCP) a hypertrophic papilla of Vater was seen (*figures 1* and *2*). After biopsy and papillotomy, bile drainage was good. Liver function returned to normal (ALP 103 U/l, γGT 55 U/l, AST 26 U/l, ALT 17 U/l, and bilirubin 3 μmol/l). Histology revealed lymphangiectasis in the lamina propria of the papilla of Vater concordant with the diagnosis of LAM (*figure 3*). Currently, almost ten years after diagnosis, the patient remains in follow-up with radiologically stable disease on treatment with gosereline and IFN-α2b. Clinical evidence of TSC was not present in this case, therefore evaluation for the TSC gene was not performed.

Figure 1. *Papilla of Vater after precut, which proved to contain lymphangioleiomyomatosis*

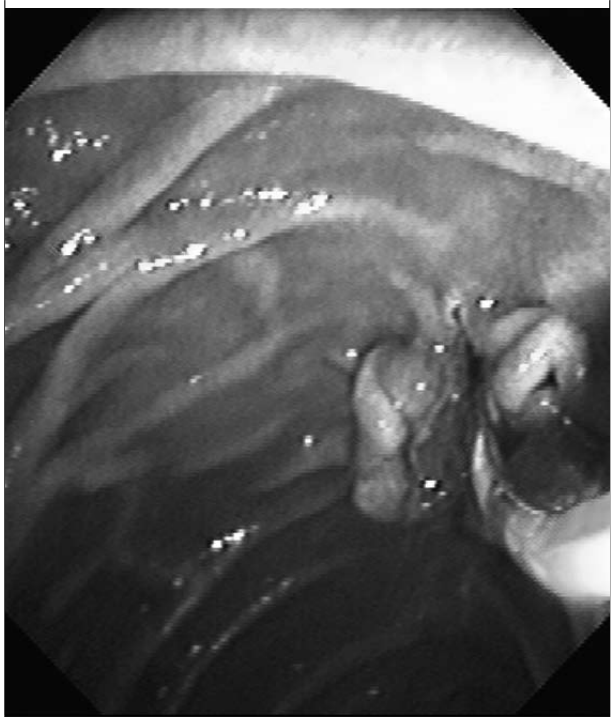


Figure 2. *Dilated bile ducts due to lymphangioleiomyomatosis of the papilla of Vater*

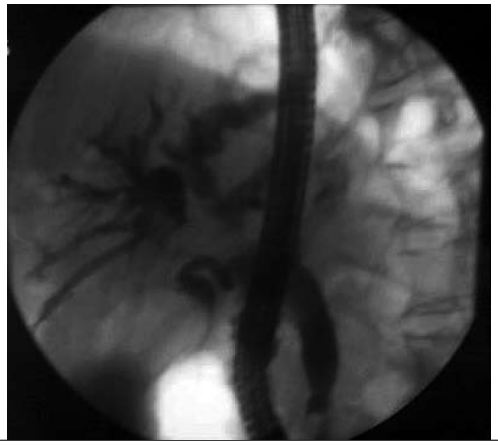
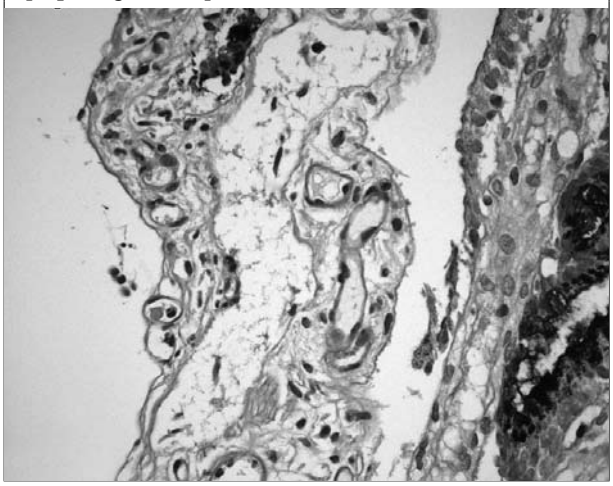


Figure 3. *Biopsy of the papilla of Vater demonstrating focal lymphangiectasis concordant with lymphangioleiomyomatosis*



DISCUSSION

This case demonstrates that LAM can occur at unexpected sites. In case of elevations of liver enzymes in patients with LAM, disseminated LAM should be considered in the differential diagnosis.

Much is still unknown regarding the natural behaviour of LAM. Patients with (sporadic) LAM generally develop progressive airflow obstruction, intermittent pneumothoraces, chylous collections or other complications. Although there are no prospective studies on survival, recent data have suggested that ten-year survival is in the order of 55 to 71%.[1] This case demonstrates that disease progression can be slowed down with a combined treatment of a GnRH agonist and IFN-α2b.

Patients who present with extrapulmonary LAM are rare. In a pathological analysis of 188 cases, extrapulmonary LAM without coexisting lung involvement was identified in only three patients (2%).[2] After reviewing the literature, we identified 24 patients who did not have lung involvement at the time of diagnosis; however, as our patient, many of these patients were later diagnosed with pulmonary LAM, usually within two years (*table 1*).[2,4-10]

The precise molecular mechanisms that modulate LAM cell growth remain unknown. LAM typically exacerbates after hormone replacement, pregnancy or oestrogen replacement and oestrogen and progesterone receptors are identified at histopathological examination.[11] These observations suggest that hormone metabolism plays a key role in LAM and most treatment concepts are now based on this suggestion. Different treatments have been tried, including oophorectomy, tamoxifen, GnRH analogues, progesterone and combinations. Radiation therapy, corticosteroids, and chemotherapy have shown little benefit.[1,12] Early institution of medroxyprogesterone is the most accepted medical treatment nowadays, although solid clinical evidence of its effectiveness is lacking. Hormonal treatment alone could not prevent disease progression in our patient. It was only when IFN-α2b was added to the treatment that the patient reached more or less stable disease (although she did develop LAM in the papilla of Vater). This case may, therefore, support the use of IFN-α2b in addition to hormonal treatment. IFN-α2b, a cytokine with antiproliferative and antiangiogenic properties, could theoretically have a place in the treatment of LAM, which is a proliferative disorder. Furthermore, recent research has demonstrated that IFN-α (which induces apoptosis) is downregulated in TSC-related and sporadic LAM providing a possible rationale for IFN-α2b treatment.[13] Recently it has been demonstrated that LAM lesions are generated by the proliferation of LAM cells with mutations leading to loss of TSC gene activity resulting in overexpression of the kinase mammalian target of rapamycin (mTOR).[12] Inhibitors of mTOR may therefore provide new treatment options.

In conclusion, we present a patient with biliary tract obstruction caused by LAM of the papilla of Vater. In patients with elevated liver enzymes and evidence of dilated bile ducts, disseminated LAM should be considered and symptoms of ampullary LAM can be treated by ERCP and papillotomy. Furthermore, our findings support the use of gosereline and IFN-α2b in patients with rapidly progressive disease and widespread lesions.

Table 1. *Cases of extrapulmonary lymphangioleiomyomatosis at diagnosis*

Reference	Age	Site	Size (cm)	Clinical features	pLAM	Follow-up (years)
Matsui *et al.*(2)	30	Pelvis	1	NA	No	5
	45	Retroperitoneal	2	Adenopathy	No	Not assessed
	53	Pelvis	NA	NA	No	36
	35	Retroperitoneal	NA	NA	No	Not assessed
	30	Pelvis	12	Pain	Afterwards*	11
	53	Retroperitoneal	2.5	NA	Afterwards*	3.5
	45	Retroperitoneal	2.5	Adenopathy	Afterwards*	5
	49	Retroperitoneal	5	Mass	Afterwards*	13
	34	Renal hilum	1	Mass	Afterwards*	7
	37	Retroperitoneal	1	NA	Afterwards*	3
	37	Retroperitoneal	20	NA	Afterwards*	6
	32	Retroperitoneal	2	Chylous ascites	Afterwards*	Not assessed
	Not known	Pelvis	NA	Mass	Not assessed	Not assessed
	Not known	Pelvis	NA	Mass	Not assessed	Not assessed
	31	Pancreas	9	Pain, diarrhoea	Afterwards*	1
	33	Perirenal	NA	Distension	Afterwards*	0.8
	29	Pelvis	5	Pain	Afterwards*	1
Jaiswal *et al.*(4)	51	Retroperitoneal	12	Radiculopathy	No	6, NED
Wong *et al.*(5)	32	Pelvis	NA	Pain	Not assessed	Not assessed
Lam *et al.*(6)	35	Pelvis	11	Leg oedema	Afterwards*	Not assessed
Kim *et al.*(7)	21	Pelvis	10	Pain	Afterwards*	6, died (pLAM)
Wan *et al.*(8)	31	Retroperitoneal	5	Mass	No	2
Atallah *et al.*(9)	44	Pelvis	22	Distension	No	NA
Kebria *et al.*(10)	59	Retroperitoneal	5.5	Vaginal bleeding	No	0.5

NED = no evidence of disease, pLAM = pulmonary lymphangioleiomyomatosis. *Patient presented with extrapulmonary lymphangioleiomyomatosis and subsequently diagnosed with pulmonary lymphangioleiomyomatosis.

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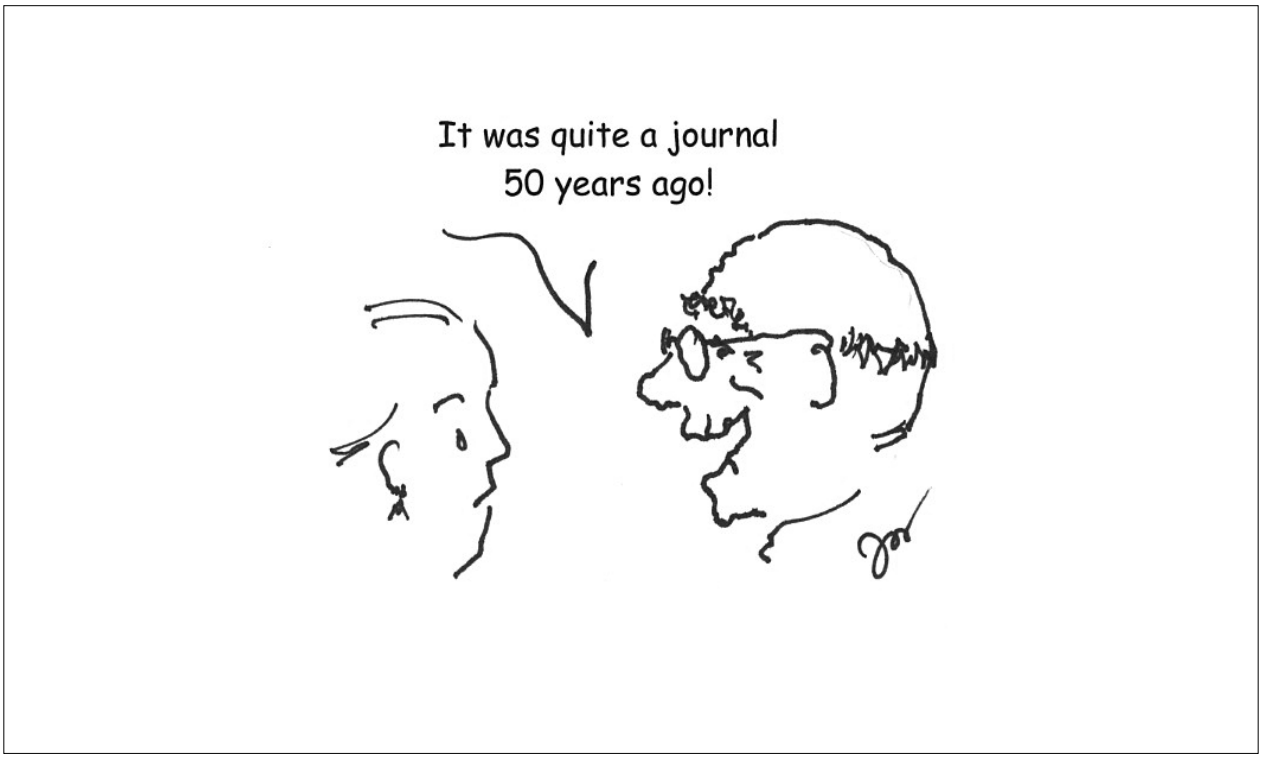

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