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Diagnostic management of occult nodal lymphangioleiomyomatosis detected during pelvic cancer staging. Localized finding or systemic disease?

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Abstract. *Background:* Lymphangioleiomyomatosis (LAM) is a neoplastic disease that generally arises in the lung (pLAM) and may be associated with "Tuberous sclerosis complex" (TSC). Occasionally, LAM can arise at the extrapulmonary sites (eLAM), such as the mediastinum, the retroperitoneum or the lymph nodes. 25-30% of the patients affected by pLAM develop eLAM. In asymptomatic patients, the presence of mediastinal and retroperitoneal eLAM preceded that of pLAM by usually 1-2 years. Nevertheless, some authors reported that the nodal eLAM, detected during pelvic cancer staging, arise in patents without pLAM and/or TSC. In this paper we review the Literature of this rare condition suggesting its diagnostic management. *Results:* To date, it has been reported 30 cases. The mean age at diagnosis is 55 years and around 30% of patients are postmenopausal. In only 2 cases was diagnosed a following p-LAM. One patient with endometrioid carcinoma and pelvic nodal eLAM reported *TSC2* germiline mutation. None case was associated with both p-LAM and TSC. *Conclusions:* The retrospective probability to have p-LAM in patients with staging pelvic nodal e-LAM is 6,6% (4/30) lower than the probability to have e-LAM in patients affected by p-LAM (25-30%). In both this association is more probable sporadically than associated with TSC. The association between cancer staging pelvic nodal e-LAM and TSC is low (3%; 1/30). The p-LAM developed are asymptomatic with a behavior, regardless of hormonal status, similar to lesions diagnosed in postmenopausal although further studies are mandatory to confirm it. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 33-38)*

Key words: pulmonary lymphangioleiomyomatosis, extrapulmonary lymphangioleiomyomatosis, tuberous sclerosis complex, pelvic cancer

Introduction

Lymphangioleiomyomatosis (LAM) is considered by WHO a low-grade destructive metastasizing neoplastic disease that generally arises in the lung (pLAM) and predominantly affect females (1). pLAM may be accompanied by symptoms such as a persistent cough, hemoptysis and chyloptysis and can be associated with the inherited syndrome "Tuberous sclerosis complex" (TSC) (2). Pulmonary lesional cells are characterized by biallelic mutations in the same gene of TSC called *TSC2* (1). Occasionally, LAM can arise at the extrapulmonary sites (eLAM), such as the mediastinum, the retroperitoneum or the lymph nodes (3). Controversy exists in the literature regarding the relationship between eLAM, pLAM

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and TSC (4). Several studies have reported eLAM in patients affected by pLAM, some of whom also had TSC. On the other hand, primary mediastinal or retroperitoneal eLAM have been identified as indicator for following pLAM (5). In this background some Authors (6) supposed that a specific eLAM consisting of occult lymph node LAM detected during surgical staging of pelvic cancer is not commonly associated with pLAM or TSC even if these patients should still be formally evaluated for both diseases (6). In this paper we review the Literature (with an additional case) about this rare condition suggesting its potential diagnostic management.

Additional case

A 44-years old Caucasian premenopausal woman diagnosed with cervical mucinous adenocarcinoma underwent surgery for radical hysterectomy PIVER3 with bilateral oophorectomy and pelvic lymphadenectomy (23 nodes isolated). The carcinoma was poorly differentiated (G3) with a maximum diameter of 3,7 cm and deepest stromal infiltration of 1,3 cm, nodal metastasis were not observed; stage IB1 according to FIGO. Histological examination revealed that four lymph node showed a neoplastic proliferation of spindle cells arranged in short fascicles "leiomyoma-like" occasionally swirling. Nuclear atypia, necrosis or mitotic activity were absent. Immunoistochemical revealed that spindle proliferating cells showed intense expression for smooth muscle actin (AML), focally for HMB45 and absent for MelanA. These characteristics were diagnostic for an incidental nodal eLAM (Fig. 1) (7,8). In adjuvant setting was performed external fields radiotherapy with VMAT technique, total 45 Gy in 25 fractions. After ten months follow-up, CT scan showed radiological features of well-defined, uniformly thin-walled cyst (maximum diameter 15 mm) that were diffusely distributed throughout both lungs (Fig. 2). According the European Respiratory Society guidelines (9) a lung biopsy was not necessary and pulmonary "definite LAM" diagnosis was produced. Lung functional tests were within the normal range and the patient was asymptomatic (Fig. 2). A TSC based on clinical criteria was excluded according the international TSC consensus group (10). A surveillance program "wait and see" was proposed and the follow up available consists of 21 months comprehensive of oncological and gynecological follow up.

Literature review

Medical Literature databases (Pubmed and Google Scholar) were searched. Inclusion criteria were: case reports and case series published before july 1st, 2017, concerning patients with "pelvic carcinoma" and/or "extrapulmonary lymphangioleyomyomatosis and/or tuberous sclerosis". Moreover, reference lists of all articles were also searched to identify additional studies.

Discussion

Pulmonary lymphangioleiomyomatosis (pLAM) is a disorder occurring almost exclusively in women, although rare cases have been reported in men with TSC. It was originally believed that lymphangioleiomyomatosis occurred primarily in women of reproductive age, but lymphangioleiomyomatosis is now increasingly recognized in postmenopausal women in whom there appear to be slower rate of disease progression. pLAM can occur sporadically or in women with TSC. Most women with sporadic LAM have renal angiomyolipoma, many have retroperitoneal and abdominal lymphadenopathy, and some have chylous pleural effusion (1). Most of extrapulmonary LAM (eLAM) occurred in lymph nodes along the lymphatic vessels of the mediastinum and the retroperitoneum with 3 major locations (decreasing frequency order): i) the posterior mediastinum, ii) the upper retroperitoneal areas close to the abdominal aorta and iii) the pelvic cavity (3).

It is thought that 25% to 30% of patients with pLAM will develop lymphatic abnormalities (lymphadenopathy or chilus ascites) visible on the abdominal CT (4). The incidence may be even higher if we consider asymptomatic clinically occult eLAM as suggested by a study performing exhaustive histopathologic examination (including autopsy) of gynecologic organs (11). So far, Chu et al. (12) reported a cohort of 35 pLAM with retroperitoneal (77%) and pelvic lymphoadenopathy (11%) whereas Urban et al. (13) found a lower incidence (24%) of abdominal lymphadenopathy in their patients. In a serie of 554

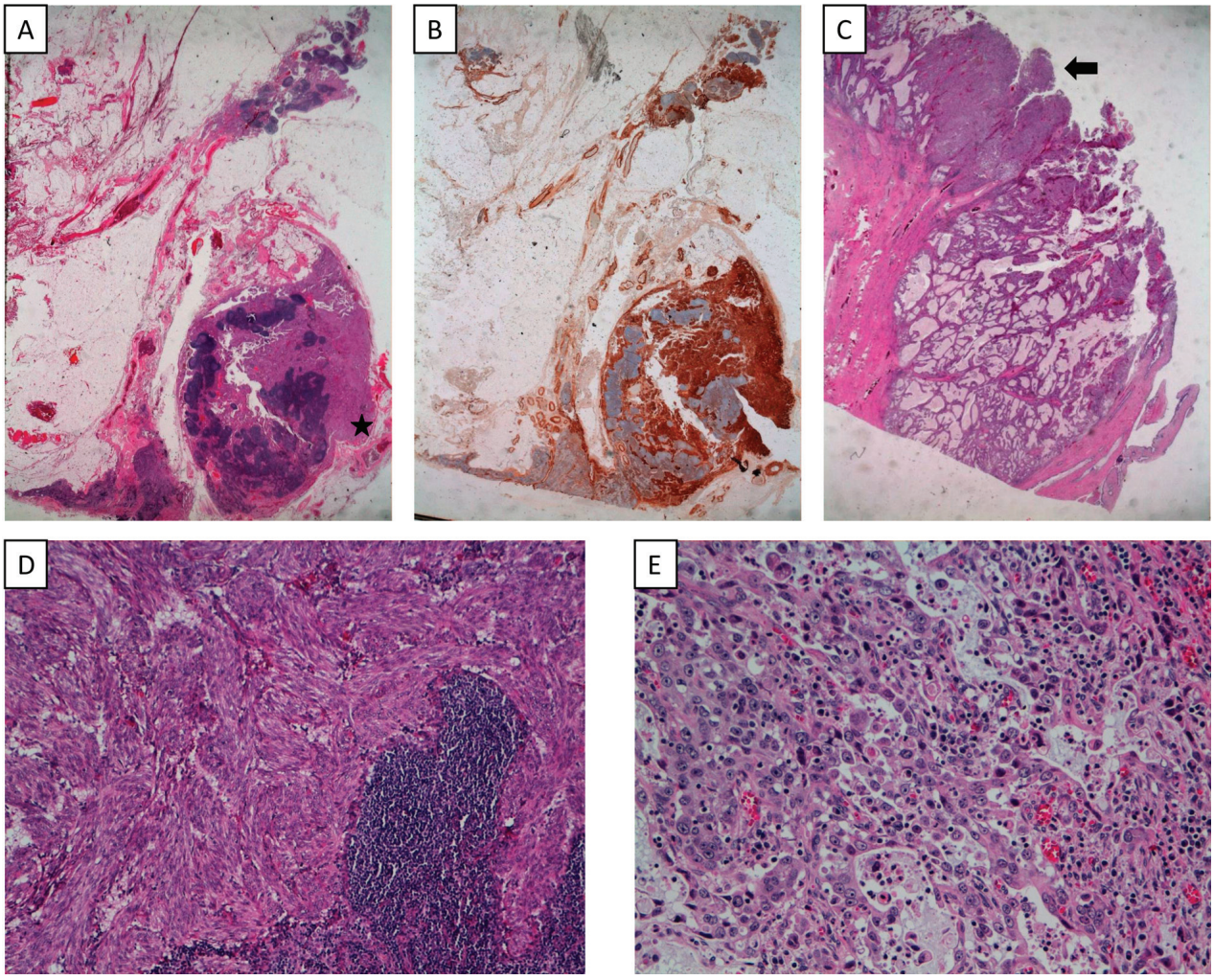
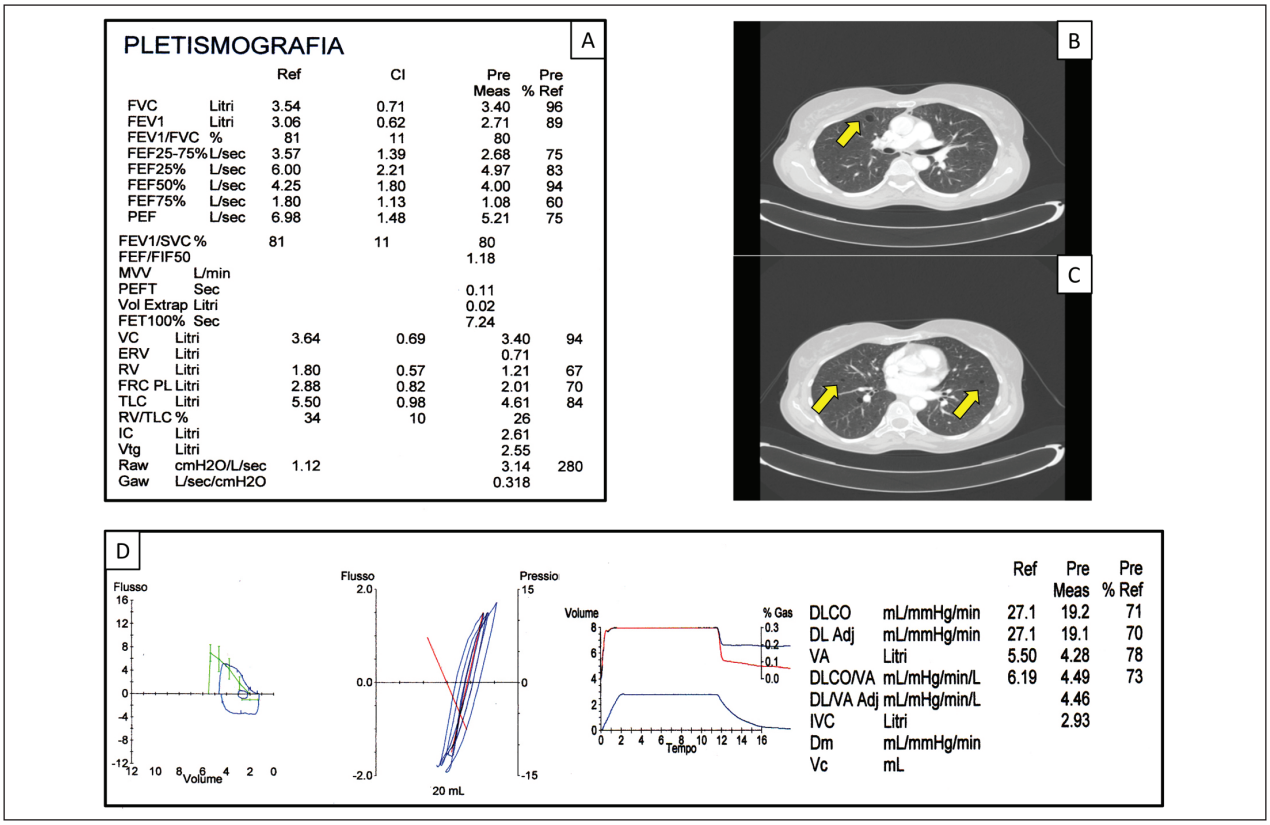


Fig. 1. Nodal and extranodal *(star)* incidental lymphangioleiomyomatosis detected during pelvic cancer staging **(A)** (10X; H&E). The lesional cells showed intense expression for smooth muscle actin **(B)** (10X; AML). Histological examination revelead spindle cells arranged in short fascicles lacking of atypia, mitosis or necrosis **(D)** (100X, H&E). Endocervical adenocarcinoma well differentiated showing a solid poorly differentiated *(arrow)* area **(C)** (10X, H&E). The carcinoma consisted of neoplastic cells whith evident atypia and mitotic activity (E) (200X; H&E).

pLAM, 189 (34%) patients were affected by eLAM stratified in 177 out of 460 (38%) sporadically and only 12 out 94 (12,8%) associated with TSC (4). This difference was statistical significant (p<0,01) and showed as the eLAM is more probable in patients without TSC (94% of all cases; 177/189) (4).

On the other hand, it's unclear whether all patients affected by primary eLAM have undiagnosed pLAM or are at risk for developing it (6). In patients entirely without signs or symptoms of pLAM, some investigators have proposed that the presence of mediastinal and retroperitoneal nodal LAM may be a high risk indicator for the development of pLAM (3). In 11 out of 16 (69%) patients reported the diagnosis of clinically significant eLAM preceded that of pLAM, established usually within 2 years (5). This was attributable to the fact that the clinical manifestations of pLAM were absent or minimal in their patients and that the corresponding radiographic changes (early cystic lesions) are evident on high-resolution CT but not on routine roentgenograms of the chest (3). Only three cases were associated with TS (19%) (5).

Recently, Rabban et al. (6) reported a specific serie of pelvic lymph node eLAM, detected incidentally during cancer staging, in which the patients



		Ref	CI	Pre Meas	Pre % Ref
FVC	Litri	3.54	0.71	3.40	96
FEV1	Litri	3.06	0.62	2.71	89
FEV1/FVC	%	81	11	80	
FEF25-75%	L/sec	3.57	1.39	2.68	75
FEF25%	L/sec	6.00	2.21	4.97	83
FEF50%	L/sec	4.25	1.80	4.00	94
FEF75%	L/sec	1.80	1.13	1.08	60
PEF	L/sec	6.98	1.48	5.21	75
FEV1/SVC	%	81	11	80	
FEF/FIF50				1.18	
MVV	L/min				
PEFT	Sec			0.11	
Vol Extrap	Litri			0.02	
FET100%	Sec			7.24	
VC	Litri	3.64	0.69	3.40	94
ERV	Litri			0.71	
RV	Litri	1.80	0.57	1.21	67
FRC PL	Litri	2.88	0.82	2.01	70
TLC	Litri	5.50	0.98	4.61	84
RV/TLC	%	34	10	26	
IC	Litri			2.61	
Vtg	Litri			2.55	
Raw	cmH2O/L/sec	1.12		3.14	280
Gaw	L/sec/cmH2O			0.318	

		Ref	Pre Meas	Pre % Ref
DLCO	mL/mmHg/min	27.1	19.2	71
DL Adj	mL/mmHg/min	27.1	19.1	70
VA	Litri	5.50	4.28	78
DLCO/VA	mL/mHg/min/L	6.19	4.49	73
DL/VA Adj	mL/mHg/min/L		4.46	
IVC	Litri		2.93	
Dm	mL/mmHg/min			
Vc	mL			

Fig. 2. Lung functional tests, within the normal range, reflect the absence of clinical syntoms **(A,D).** CT scan showed well defined, thin walled cyst *(arrow)* diffusely distribuited throughout both lungs. A lung biopsy was not necessary and pulmonary "definite LAM" was diagnosed **(B,C)**.

don't have or develop pLAM. In this scenario, the patient age can be used as a surrogate to predict the likelihood of pLAM. Because the natural history of pLAM is to progress to respiratory failure within 10 years of diagnosis, and because the most of pLAM are diagnosed around the age of 35 years, it is unlikely that neoplastic patients in their fifth decade or older without respiratory failure have pLAM or will develop it (6). To date, in Literature it has been reported (with current case) 30 pelvic nodal eLAM detected incidentally during cancer staging (Tab. 1) (2,6,14-16). The specific-organ cancer were uterine (19), ovarian (4) and bladder carcinoma (1). Six cases were squamous cervical cancer and only the current case an adenocarcinoma. (Fig. 1). The mean age at diagnosis was 55 years and around 30% of patients were postmenopausal. The probability to have or develop pLAM is 6,6% with only 2 cases diagnosed after e-LAM. These patients were asymptomatic and the presence of pLAM was not correlated with a specific hormonal status. In all cases a thoracic TC was performed within the first year after the diagnosis of nodal e-LAM and in the positive cases a lung biopsy was not necessary to diagnose the "definite LAM" (14). None case was associated with both pLAM and TSC. The report of a patient died for respiratory failure caused by late-onset symptomatic pLAM (83y) in which was diagnosed autoptically concomitant cervical carcinoma and nodal eLAM (11), suggests the necessity of a long surveillance.

About the question whether TSC patients have an increased risk of developing malignant tumors, a systematic analysis of malignancies in TSC patients is still lacking. Between the TSC, the rate of patients that have developed cancer in their lives is 6,25% against the prevalence percent of cancer in italian population of 4,4% (17). TSC patients do not seem to have an increased risk of developing malignant tumors besides renal cancer but when malignancies develop, age at cancer is younger than in the

Table 1. Cases of pelvic carcinoma associated with eLAM and/or TSC reported in Literature.
In the table are reported the clinical features of patients affected by pelvic carcinoma in association with eLAM and/or TSC.

Authors (year)	Cancer type	eLAM	pLAM	TSC (Germinal test)	Hormonal status (Age)
Iwasa et al. (16) (2011)	2 uterine corpus carcinoma 1 cervical squamous carcinoma	3\3	0\3	0\3	pre (47); post (70); post (59)
Ruiz-Molina et al. (14) (2013)	1 uterine corpus carcinoma	1\1	1\1 (A)	0\1	post (72)
Song et al. (2) (2014)	1 cervical squamous carcinoma	1\1	0\1	0\1	NA (46)
Suzuki et al. (15) (2016)	1 uterine corpus carcinoma	1\1	0\1	0\1	pre (47)
Remo et al. (2017)	1 cervical adenocarcinoma	1\1	1\1 (A)	0\1	pre (44)
Gyure et al. (20) (1995)	1 ovarian carcinoma and uterine corpus carcinoma	0\1	0\1	1\1 (B)	pre (29)
Wataga-kaneda et al. (19) (2013)	1 uterine cancer	0\1	NA	1\1 (B)	NA
Rabban et al. (6) (2015)	15 uterine corpus carcinoma 4 ovarian carcinoma 3 cervical squamous carcinoma 1 bladder carcinoma	23\23	0\23	1\23 (B) *(TSC2)*	pre - post (56)(31-79)
Jaffe et al. (18) (2015)	1 uterine corpus carcinoma	0\1	0\1	1\1 (B)	pre (39)
Peron et al. (17) (2017)	2 cervical squamous carcinoma	0\2	0\2	2\2 (A) *(TSC1; NM)*	pre (44); pre (36)

eLAM= extrapulmonary lymphangioleiomyomatosis; pLAM= pulmonary lymphangioleiomyomatosis; TSC Tuberous sclerosis complex; B= before cancer diagnosis; A=after cancer diagnosis; pre= premenopausal; post= postmenopausal; NA= not available

general population and malignant tumors are more frequently diagnosed in patients with mutations in TSC1 when compared to TSC2 and NM1 (17). In literature are reported six cases of pelvic carcinoma associated with TSC (Tab. 1) (6, 17-20). Three cases underwent to germinal test. One patient with endometrioid carcinoma and pelvic nodal incidental eLAM reported *TSC2* germiline mutation (6). The other two patients with TSC pelvic cancer, lacking of nodal eLAM, showed *TSC1* mutation and *NM*. In four patients with mental retardation the diagnosis of TSC was before the cancer whereas in two patient the TSC was diagnosed 4 and 5 years after (17).

Because eLAM may precede both TSC and pLAM, and because only a minority of patients with eLAM seek evaluation for TSC or pLAM by clinical medical genetics service, in a pratical perspective, the pathologist should document the possibility, albeit low, of pLAM or TSC when staging pelvic lymph node LAM is diagnosed (6) as introduced in other inherited pathology (Universal Screening for Lynch syndrome) (21). In this scenario the role of pathologist consist in the identification of lesions potentially caused by inherited genetic syndrome in order to enrol patient and relatives in specific screening program (22).

In conclusion, the retrospective probability to have pLAM in patients with pelvic nodal LAM detected during cancer staging is 6,6% (4/30) lower than the probability to have eLAM in patients affected by pLAM (25-30%). In both this association is more probable sporadically than associated with TSC. The association between cancer staging pelvic nodal eLAM and TSC is low (3%; 1/30) and reported associated with *TSC2* germinal mutation. The pLAM developed are asymptomatic with a behavior, regardless of hormonal status, similar to lesions diagnosed in postmenopausal althought further studies are mandatory to confirm it. The pathologist in all this cases should be suggest the possibility (low) of pLAM or TSC. The clinician should propose, within two years, a pulmonary TC to detect eventually pLAM and a close follow up (4-6 years) for excluding clinically TSC criteria. The management should be included a bland long surveillance to evaluate potential late-onset symptomatic pLAM. The routinely use of TSC germinal test is to avoid in this subset of eLAM.

References

1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson A. WHO Classification of tumor of the Lung, Pleura, Thymus and Heart. 4Th ed.; 2015: IARC press.
2. Song DH, Choi IH, Ha SY, et al. Extrapulmonary lymphangioleyiomioma: Clinicopathological Analysis of 4 cases.Kor J Path; 2014:48: 188-192.
3. Matsui K, Tatsuguchi A, Valencia J, et al. Extrapulmonary lymphangiomyomatosis (LAM): clinicopathologic Features in 22 cases. Hum Path 2000; 31(10): 1242- 1248.Am j Surg Path 2015; 39(8): 1015-1025.
4. Johnson SR, Taveira-Silva AM, Moss J. Lymphangiomyomatosis. Clin chest med 2016 ; 37: 389-403.
5. Jaiswal VR., Baird J., Fleming J., Miller DS., Sharma S., Moelberg K. Localized retroperitoneal lymphangioleyomyomatosis mimicking malignancy. Arch Pathol Lab Med 2003; 127: 879-882.
6. Rabban JT, Firetag B, sangoi AR, Post M, Zaloudek CJ. Incidental Pelvic and Paraaortic Lymphnode Lymphangiomyomatosis detected during surgical staging of pelvic cancer in women without symptomatic pulmonary Lymphangiomyomatosis ot tuberous sclerosis complex.
7. Pea M, Martignoni G, Zamboni G, Bonetti F. Perivascular epithelioid cell. Am J Surg Pathol. 1996 Sep;20(9):1149-53. No abstract available.
8. Martignoni G, Pea M, Reghellin D, Gobbo S, Zamboni G, Chilosi M, Bonetti F. Molecular pathology of lymphangioleiomyomatosis and other perivascular epithelioid cell tumors. Arch Pathol Lab Med 2010 Jan; 134(1):33-40. doi: 10.1043/2008-0542-RAR1.1.
9. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, Reynaud-Gaubert M, Boehler A, Brauner M, Popper H, Bonetti F, Kingswood C and the Review Panel of the ERS LAM Task Force. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 2010; 35: 14–26
10. Northrup H, Krueger DA, and on behalf of the International Tuberous Sclerosis Complex Consensus Group Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference *Pediatr Neurol*. 2013 October ; 49(4): 243–254. doi:10.1016/j.pediatrneurol.2013.08.001.
11. Hayashi T, Kumasaka T, Mitani K, Terao Y, Watanabe M, Oide T, Nakatani Y, Hebisawa A, Konno R, Takahashi K, Yao T, Seyama K. Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients.
12. Chu S, Horiba K, Usuki J, Avila N, Chen CC, Travis WD, Ferrans VJ, Moss J. Comprehensive evaluation of 35 patients with Lymphangiomyomatosis. Chest 1999; 115(4): 1041-1052.
13. Urban T, Lazor R, Lacronique J, et al. Pulmonary lymphangioleiomyomatosis: A study of 69 patients. Medicine 78:321-337, 1999.
14. Ruiz-Molina I, Civico-Amat V, Solis-Garcia E. Extrapulmonary lymphangiomyomatosis in pelvic lymphoadenectomy associated with invasive endometrial carcinoma. Rev Esp Patol 2014; 47(3): 193-196.
15. Suzuki K, Nagasaka K, Oda K, et al. A case of lymphangiomyomatosis associated with endometrial cancer and severe systemic lupus erythematosus. Bmc Cancer 2016; 16: 390-395.
16. Iwasa Y, Tachibana M, Ito Het al. Extrapulmonary lymphangioleiomyomatosis in pelvic and paraaortic lymph nodes associated with uterine cancer: a report of 3 cases. Int J Gynecol Pathol. 2011 Sep;30(5):470-5
17. Peron A, Vignoli A, Labriola F, et al. Do patients with tuberous sclerosis complex have an increased risk for malignancies? Am J Med Genet A. 2016 Jun; 170(6):1538-44. doi: 10.1002/ajmg.a.37644. Epub 2016 Apr 7
18. Jaffe JS, Chambers JT. Endometrial carcinoma presenting in a premenopausal patient with tuberous sclerosis. J Intellect disabil Res 2005; 49:463-465.
19. Wataya-Kaneda M, Tanaka M, Hamasaki T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: an epidemiological study of 166 Japanese patients. PLoS One. 2013 May 17;8(5):e63910. doi: 10.1371/journal.pone.0063910. Print 2013.
20. Gyure KA, Hart WR, Kennedy AW. Lymphangiomyomatosis of the uterus associated with tuberous sclerosis and malignant neoplasia of the female genital tract: a report of two cases. International Journal of Gynecologic Pathology 1995; 14: 344-351
21. Remo A, Fassan M, Lanza G. Immunohistochemical evaluation of mismatch repair proteins in colorectal carcinoma: the AIFEG/GIPAD proposal. Pathologica. 2016 Sep;108(3):104-109.
22. Remo A, Pancione M, Zanella C, Vendraminelli R. Molecular pathology of colorectal carcinoma. A systematic review centred on the new role of the pathologist. Pathologica. 2012 Dec;104(6):432-41. Review.