Incidental pelvic lymphangioleiomyomatosis in case of uterine carcinoma. Report of the case and search for similar lesions in series of staging lymhadenectomies

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A rare case of extrapulmonary nodal lymphangioleiomyomatosis (LAM) is described. In 75-ys-old woman with uterine endometrioid carcinoma FIGO grade 2, stage II, two minute lesions were found in pelvic lymph nodes by examination of routinely sampled lymph nodes (for staging purposes). Both tumors were minute and histologically inconspicuous, resembling strongly a tangentially sectioned muscular vessel or a focal fibrosis with myofibroblasts. Immunophenotype was, however, typical of lymphangioleiomyoma, with positivity for HMB45, smooth muscle actin, estrogen receptor and desmin, indicating perivascular epithelioid cell (PEC) differentiation. Additional clinical work-up did not show any signs of tuberous sclerosis, pulmonary lymphangioleiomyomatosis or another PEC-oma. To ascertain an incidence of nodal lymphangioleiomyomatosis in pelvic, retroperitoneal or peritoneal lymph nodes, a retrospective search for similar minute lesions was performed in a series which included 100 cases of gynecologic carcinomas and 25 cases of colorectal carcinomas in women. LAM was not found in any case, indicating that the lesion is very rare. Pathologic diagnosis and possible clinical significance of incidental lymphangioleiomyomatosis are discussed.
Keywords: lymphangioleiomyomatosis, lymph node, carcinoma, uterus, colon

Incidentálna pelvická lymfangioleiomyomatóza pri karcinóme maternice. Opis prípadu a pátranie po podobných léziách v súboroch stagingových resekcií
Opísaný je zriedkavý extrapulmonálny prípad lymfangioleiomyomatózy (LAM) lymfatických uzlín panvy, ktoré boli odstránené v rámci stagingovej operácie pre karcinóm uteru. Šlo o 75-ročnú pacientku s endometrioidným karcinómom tela maternice, FIGO grade 2, stage II. Lézie boli nájdene v dvoch pelvických uzlinách. Boli drobné, histologicky málo nápadné a napodobňovali hyperpláziu myofibroblastov puzdra uzliny alebo tangenciálny rez steny muskulárnej cievy. Imunohistochémia však ukázala expresiu HMB45, estrogénových receptorov a desmínu, čo svedčilo o „perivascular epithelioid cell" (PEC) diferenciácii a viedlo k diagnóze lymfangioleiomyomatózy. Následné klinické vyšetrenia vylúčili u pacientky tuberóznu sklerózu, pulmonálnu lymfangioleiomyomatózu alebo iný PEC-óm. Kvôli zisteniu, ako často sa vyskytuje incidentálna lymfangioleiomyomatóza lymfatickej uzliny, bol vyšetrený archívny súbor prípadov, ktorý zahrnoval 100 prípadov karcinómov corpus uteri a ovária a 25 prípadov karcinómov hrubého čreva u žien. Nebol nájdený žiadny ďalší prípad, čo svedčí o raritnom charaktere lézie. V práci sa ďalej diskutuje o diagnóze incidentálnej LAM lymfatickej uzliny a klinickej signifikancii tohto nálezu.
Kľúčové slová: lymfangioleiomyomatóza, lymfatická uzlina, karcinóm, uterus, hrubé črevo

Newslab, 2018; roč. 9 (1): 8 – 11

Introduction

Lymphangioleiomyomatosis (LAM) is a rare lesion composed of so-called perivascular epithelioid cells (PEC)[1-5]. LAM occurs typically in the lung of premenopausal women, and it is sometimes associated with tuberous sclerosis. LAM in extrapulmonary location is exceedingly rare, being reported in pelvis, retroperitoneum, uterus, mesentery, kidney hilus, and liver[6-9]. Recently, Rabban et al. and Schoolmeester and Park described new 44 cases of nodal LAM which had been found incidentally by examination of retroperitoneal and pelvic lymph nodes removed at staging surgery for gynecologic cancers[10,11]. In our practice, we have seen one similar incidental LAM in patient with uterine endometrioid carcinoma. We present this case here. In addition, we wondered whether minute and histologically inconspicuous LAM cannot be more frequent in lymph nodes, and therefore we search for it in our files, examining a series of lymph nodes removed for gynecologic and colorectal carcinomas. Our results show that incidental LAM in this clinico-pathological context represents a rare lesion.

Material and methods

In the case of incidental LAM, routine examination of formalin fixed paraffin embedded tissue was performed. After finding of possible LAM in two lymph nodes, following immunohistochemical stains were performed: HMB-45 (clone HMB-45), melan-A (clone A123), alpha-smooth muscle actin, h-caldesmon, progesterone receptor, estrogen receptor, desmin, D2-40, CD31, pancytokeratin AE1/AE3, and S100 protein (all from Dako, Copenhagen, Denmark). Immunostaining was performed according to standard protocols using streptavidin-biotin complex labelled with peroxidase (Dako, Copenhagen, Denmark). The positive and negative controls were applied. The subsequently examined series of lymph nodes was selected from our routine files. We examined lymph nodes in 57 cases of uterine carcinoma and in 47 cases of ovarian carcinoma. Age of these gynecologic patients ranged from 40 to 83 years, average age was 63.3 years. Average number of lymph nodes per patient was 46, ranging from 12 to 99 nodes. In addition, lymph nodes of colorectal carcinomas of female patients were reviewed. This series included 25 women, with age range 50-87 years and average age 71.4 years. Altogether, 4595 lymph nodes were reviewed in the study. The capsule of lymph nodes often contains myoid cells and muscular appearing vessels, and this morphology mimics minute LAM. Therefore, in 32 selected lymph nodes from 32 patients, immunostains for HMB45 and melan-A were performed.

Results

LAM was found incidentally in a 75-ys-old, para 2, gravida 2 patient. She underwent a hysteroscopy, dilatation and curettage for metrorrhagia. The medical history of the patient included complex endometrial hyperplasia without atypia diagnosed 18 years and 10 years ago, respectively. Histological examination of the current curettage specimen showed endometrioid carcinoma (EC) FIGO grade 2, and therefore a total hysterectomy with bilateral salpingo-oophorectomy was performed. Because an intraoperative biopsy showed EC infiltrating 60% of the myometrial thickness, the pelvic and paraaortic lymph nodes were removed. **Histologically**, the tumor was EC FIGO grade 2, with initial infiltration of the endocervix. No features of LAM were found in the myometrium. Both adnexa did not contain any tumor or microscopic LAM. Among 43 removed lymph nodes, lymphangioleiomyoma was found in one of 9 right obturator nodes and in one of 7 left obturator nodes, respectively. The lesions measured 1,5 mm and 1 mm, respectively, and both were associated with lymph node capsule, mimicking strongly a focal reactive fibrosis or a tangentially sectioned wall of a muscular vessel. They were composed of spindle to ovoid cells, with bland appearing nuclei, small nucleoli, and without mitotic activity ***(Figure 1)***. A few of the nuclei were cigar shaped or showed mild symplastic-type pseudoatypia. The cytoplasm was eosinophilic to clear. The tumor cells created small groups and fascicles. In addition, the lesions contained numerous capillary sized, thin walled and partly dilated vessels. **Immunohistochemically**, the cells were positive for HMB45, alpha-smooth muscle actin, h-caldesmon, and estrogen receptor ***(Figure 2)***. Desmin was expressed only by scattered cells ***(Figure 2e)***. Endothelium of the vessels was positive for both CD31 and D2-40 ***(Figure 2f)***. Following antibodies gave negative results in tumor cells: pancytokeratin AE1/AE3, melan-A, progesterone receptor, S100 protein. A diagnosis of incidental LAM was rendered. Subsequent clinical examinations did not find any signs of tuberous sclerosis, pulmonary LAM or another PEC-oma. For EC, the patient received external adjuvant radiotherapy, and she is without recurrence 16 months after the surgery.

In the series of 100 gynecologic and 25 colorectal carcinomas, no case of LAM was found. We have often seen myoid cells and muscular appearing vessels in the region of the capsule of the lymph node, and this finding was sometimes suspicious for LAM. However, HMB45 and melan-A performed in 32 of such cases gave negative results.

Discussion

Lymphangioleiomyomatosis (LAM) is an abnormal proliferation of PECs around lymphatic vessels (PEC)[1-5]. PEC is an enigmatic cell that has no normal counterpart and that shows myomelanotic phenotype with expression of melanocytic and myoid antigens[1-4]. In addition to LAM, PEC differentiation occurs in several other tumors, all of which can be associated with tuberous sclerosis complex[1-5]. This PEComa

Figure 1. *Histological features of nodal LAM.* ***(a)*** *At low power, the spindle cell lesion resembles a reactive fibrous thickening of the capsule of lipomatous lymph node.* ***(b)*** *High-power shows spindle and epithelioid cells with numerous vessels.*

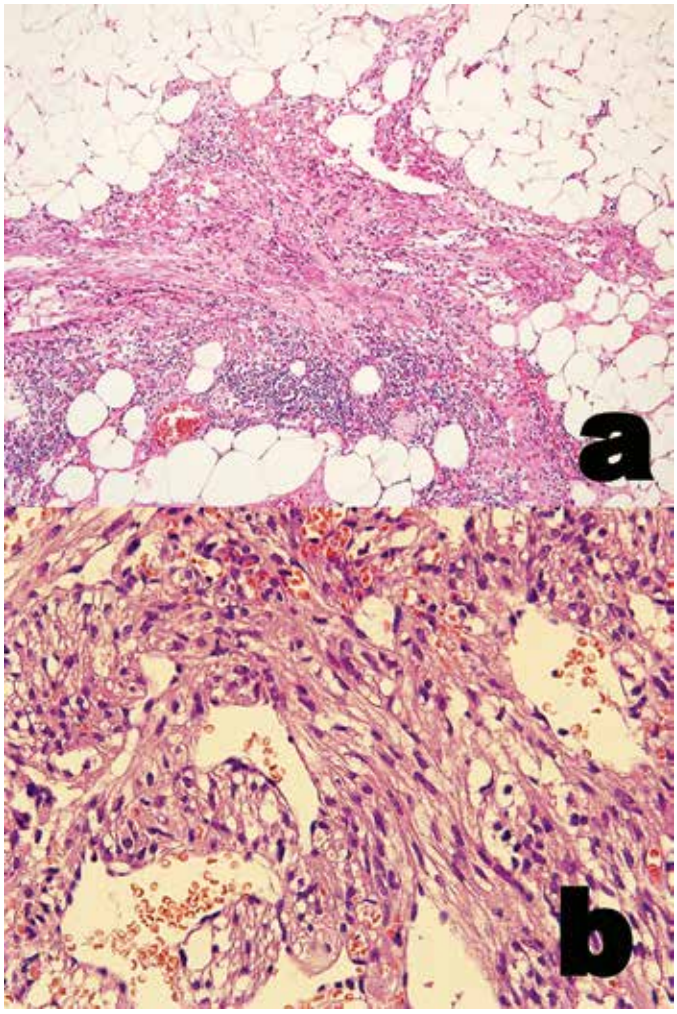
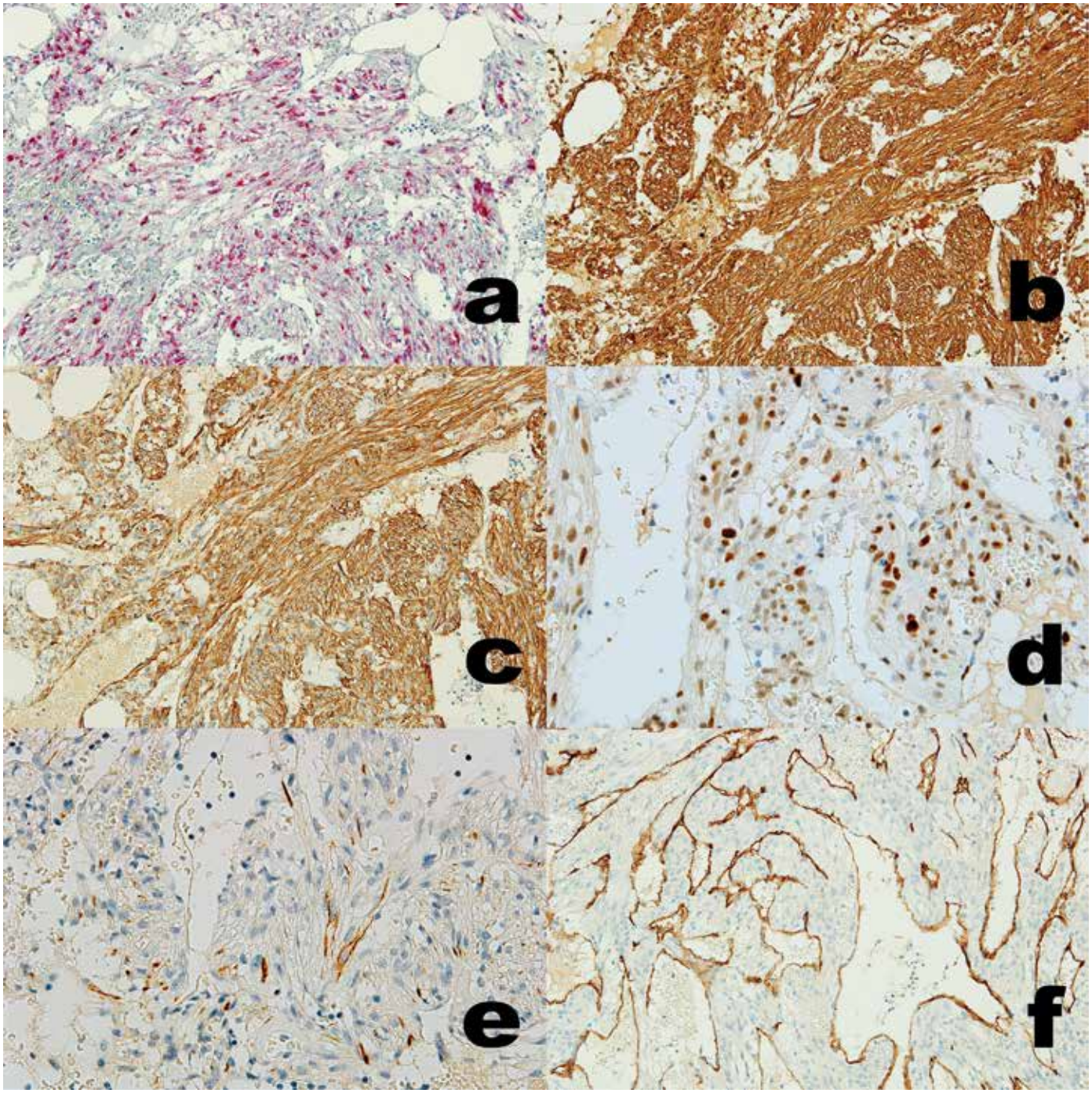


*Figure 2. Immunohistochemical features of nodal LAM. **(a)** HMB-45 positivity. **(b)** Alpha-smooth muscle actin positivity. **(c)** H-caldesmon expression. **(d)** Estrogen receptor positivity. **(e)** Desmin expression is seen in scattered cells. **(f)** D2-40 is positive in the endothelium of the vessels.*



"family" includes LAM, renal and extrarenal angiomyolipoma, pulmonary and extrapulmonary sugar tumor, myomelanotic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of PECs, renal capsular leiomyoma, and other tumors with similar features at various sites and with various biological behavior (an excellent review of PEComas was done recently by Thway and Fisher)[2]. In our case, morphological finding of myoid-appearing spindle cells, rich lymphatic vasculature and immunohistochemical proof of PEC differentiation are typical for LAM. As mentioned above, extrapulmonary LAM is rare lesion which can be associated with tuberous sclerosis and/or with pulmonary LAM[7]. Schoolmeester and Park and Raban et al. found recently, that LAM is sometimes present in lymph nodes removed at staging surgery for gynecologic carcinomas. Our case of incidental LAM is quite similar to those described by Schoolmeester and Park and Raban et al.[10,11]. After these studies were published in October 2015, we started to search for minute LAM by examination of all lymph nodes removed in gynecologic staging procedures. In addition, we performed retrospective search in our archive. Finally, our series included 100 cases of gynecologic carcinomas and 25 cases of female colorectal carcinomas. However, we did not find any additional incidental LAM. Thus, our results show that the lesion must be

rare. Schoolmeester and Park and Raban et al.[10,11] described together 44 cases and this number could indicate that incidental LAM is quite frequent. However, abovementioned two group of authors did not study incidence of incidental LAM, because their data did not include overall number of their resectates. Schoolmeester and Park[10] found 18 cases among their resections performed over 11-year period in Memorial Sloan Kettering Cancer Center in New York, probably the institution with busy gynecologic surgery service. In study of Raban et al.[11], many of their 26 cases were examined in consultation, and this fact can explain relatively high number of their cases.

Our experience with incidental LAM shows that it is quite inconspicuous or occult by microscopic examination. Microscopic LAM can be easily overlooked, because it has bland spindle cell and reactive appearance, and, moreover, the pathologists are focused by examination of lymph nodes on search for metastatic carcinoma. Histologically, the lesions resemble reactive foci composed of bland myofibroblasts, with myoid-appearing spindle cells and rich vasculature. Small focus of LAM can also mimic tangentially sectioned wall of small muscular vessel. However, at least some cells show epithelioid or clear cell morphology of PEComa in addition to predominant myoid cells, and their immunophenotype indicates PEC differentiation, with positivity for HMB-45, melan-A, smooth muscle actin, desmin, and beta-catenin[1-5,10,11].

The clinical significance of incidental LAM in retroperitoneal/pelvic lymph nodes seems to be marginal in the context of present gynecologic malignancy. However, the finding is certainly not fully insignificant. The patient with extrapulmonary LAM has still a small risk for tuberous sclerosis and/or pulmonary LAM[7]. Although in Schoolmeester and Park´ series of incidental LAM none of the patients had tuberous sclerosis or pulmonary LAM, the series of Raban et al. includes two cases with tuberous sclerosis complex[11]. In sum, only two of 45 cases of incidental nodal LAM reported till now (including our case) were associated with tuberous sclerosis complex, which represents a risk 4.4%. Although this risk is low, we concur with Raban et al.[11] that patient with incidental LAM should be formally examined for tuberous sclerosis and pulmonary LAM.

In conclusion, we have described incidental LAM in pelvic lymph nodes. Our case shows that minute LAM can be quite inconspicuous by microscopic examination and that immunohistochemistry is very helpful for diagnosis. In addition, we searched for incidental LAM in series of 125 staging lymphadenectomies performed for gynecologic and colorectal carcinomas. We did not find any further case of LAM, and this result indicates that incidental LAM represents rare finding.

Acknowledgement: *The authors acknowledge the support provided by OP Research and Development: Building additional technical infrastructure in research of diagnostic procedures and methodology in early diagnostics of most frequent oncological diseases in women, project ITMS 26210120026, using the financial assistance from the European Regional Development Fund.*

Poďakovanie: *Tento článok vznikol vďaka podpore v rámci OP Výskum a vývoj pre projekt: Dobudovanie technickej infraštruktúry v oblasti výskumu diagnostických postupov a metód v rámci včasnej diagnostiky najčastejších onkologických ochorení u žien, ITMS 26210120026, spolufinancovaný zo zdrojov Európskeho fondu regionálneho rozvoja.*

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