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Characterization of leiomyomatoid angiomatous neuroendocrine tumour (LANT)-like tumour of the myometrium with histopathological examination.

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ABSTRACT

Leiomyomatoid angiomatous neuroendocrine tumour (LANT) is a possible new disease entity that was described as a dimorphic neurosecretory tumour with a leiomyomatous vascular component; it was found in the pituitary. We describe here uterine LANT-like tumour in a 45-year-old woman with uterine mesenchymal tumour, diagnosed clinically as uterine leiomyoma. She underwent laparoscopic myomectomy. The tumour consisted of hyalinized vasculature, containing factor VIII-positive endothelium and smooth muscle actin-positive vascular smooth muscle cells, and stromal cells, expressing neuroadhesion molecules. Both vascular and stromal components diffusely expressed chromogranin A. Histopathological examinations of uterine LANT-like tumour revealed the common characteristic abnormalities of uterine mesenchymal malignant tumours, i.e. leiomyosarcomas. Our research findings show that defective expression of CALPONIN h1 and proteasome beta 9 (PSMB9)/b1i is observed in uterine LANT-like tumour such like immune-pathological findings of uterine leiomyosarcoma. These findings meet the definition of uterine LANT-like tumour, and the occurrence of our case suggests that LANT is a special type of neuroendocrine neoplasm and is not organ specific.

KEYWORDS : Leiomyosarcoma; PSMB9/b1i; CALPONIN h1; LANT; Leiomyosarcoma

Introduction

Leiomyomatoid angiomatous neuroendocrine tumour (LANT) was firstly reported as a new neoplastic category [1]. Histopathologic concept of LANT is that of a dimorphic neoplasm consisting of an admixture of neurosecretory cells and leiomyomatous stroma surrounding intratumour vessels [1]. The original case was reported as a pituitary neoplasm. Histopathological studies with LANT revealed 2 major tumour components [1]. The first cell population comprised cytokeratin-negative neuroendocrine cells positive for neuroadhesion molecules and chromogranin A as a serum marker of neuroendocrine tumours [1]. The second constituent was a smooth muscle actin-positive leiomyomatous vascular component associated with a cell-cell adhesion factor, CD34-positive endothelia [1]. On the basis of this particular histopathologic pattern and immunophenotype, our research group proposed the descriptive diagnosis of LANT and suggested that it may be a variant of a dimorphic pituitary neoplasm, possibly related to null cell adenoma. Because no additional reports demonstrate whether LANT is a pituitary-specific tumour or a type of soft tissue tumour is unclearly understood. We report here histopathological examinations of uterine LANT-like tumour revealed the common characteristic abnormalities of uterine leiomyosarcomas. This dimorphic tumour contained both vascular and stromal components. We suggest that uterine LANT-like tumour may be derived from neuroendocrine cells that may have differentiated into uterine smooth muscle cells under the influence of transforming growth factor-b (TGF-b).

Loss of PSMB9/b1i and CALPONIN h1 in uterine LANT-like tumour

During the course of an annual health examination, a healthy 45-year-old woman was found to be anemic, and a gynaecologist found a uterine tumour causing hypermenorrhea. The radiologic diagnosis was uterine leiomyoma with partial degeneration. At the patient's request, laparoscopic myomectomy was performed, the soft white tumour had a cauliflower-like surface, which was incompatible with the radiologic diagnosis. Histologically, the tumour possessed 2 major components: first, a prominent vasculature with small lumina and hyalinized walls, and, second, a cellular stromal component. Specifically, we noted oval- or spindle shaped nuclei with fine chromatin and faint nucleoli, obscure cytoplasm, and very poor mitotic activity. All randomly obtained histopathologic samples from 15 different paraffin blocks showed the same histopathologic pattern.

Smooth muscle cells in a benign mesenchymal tumour, uterine leiomyoma markedly express α-smooth muscle actin and neuroadhesion molecule (Cd56); however, no cell was positive for neuron-specific enolase, chromogranin A. Most cells of uterine LANT-like tumour diffusely express CD56 and chromogranin A [2]. In addition, the cytologic features of each major component were quite similar. We demonstrates differential expression of several proteins in human uterine mesenchymal tumours and normal myometrium. IHC examinations with uterine mesenchymal tumours demonstrated that although CALPONIN h1 and proteasome *beta* subunit (PSMB9)/b1i markedly expressed in three types of uterine mesenchymal tumors and normal myometrium, loss of expression of CALPONIN h1 and PSMB9/b1i is observed in human uterine leiomyosarcoma. We therefore examined expression pattern of both proteins, CALPONIN h1 and PSMB9/b1i in uterine LANT-like malignant tumour. IHC examination demonstrated that although CALPONIN h1 and PSMB9/b1i markedly expressed in normal myometrium, loss of CALPONIN h1 and PSMB9/b1i is observed in uterine LANT-like tumour such like immune-pathological findings of uterine leiomyosarcoma. In section of uterine LANT-like tumour, the vascular structure was reportedly composed of factor VIII-, CD31-, and CD34-positive endothelial cells, and a-smooth muscle actin and sarcomeric muscle actin-positive vascular smooth muscle cells [2,3]. Results for a lymphatic endothelial marker D2-40 were reportedly negative, suggesting that the vascular structure was not a lymphatic tumour such as lymphangiomyoma [4].

Discussion

Here, we presents histologic and immune-pathologic characteristics of a complex, dimorphic neurosecretory tumour possessing a smooth muscle cell-rich vascular component and a population of stromal cells expressing neuronal differentiation markers. On the basis of its particular histologic aspects and immune-pathologic observations, we first ruled out the possibility of a uterine leiomyoma with a heterologous paraganglioma element [5]. We also ruled out the possibility that the tumor was a glomangioma, perivascular epithelioid cell tumour, paraganglioma, solitary fibrous tumour, or extragastrointestinal stromal tumour with neuroectodermal differentiation [6-11]. Therefore, histological examinations of the uterine LANT-like tumour revealed the common characteristic abnormalities of LANT, which was reported as a pituitary neoplasm [1]. Although the characteristics of the uterine tumour were indeed those of a LANT, we found 2 significant differences between the original LANT described by Vajtai *et al*. and our clinical case [1]. First, the original LANT was identified as a pituitary

neoplasm, but our case was a uterine mesenchymal tumour. Soft tissue tumours are known to appear in various organs, including the pituitary and uterus. Instead, it may be a soft tissue tumour with a neurosecretory phenotype. Therefore, we accepted the possibility that the tumour described here was a second case of LANT. Second, in the original LANT report, chromogranin A and synaptophysin were predominantly detected in a neurosecretory component of the tumour. However, most tumour cells in uterine LANT-like malignant tumour expressed chromogranin A but not synaptophysin. Thus, tumour cells in the present case were neuroendocrine regardless of their location, whether vascular or stromal. In the initial report, a few stromal leiomyomatoid cells appeared to express chromogranin A [1]. Synaptophysin and chromogranin A, both of which are neuroendocrine marker molecules, are localized in distinctive neurosecretory vesicles, the former predominantly in small transparentlooking vesicles and the latter in large dense-cored granules [12]. It seems that part of the leiomyomatous stromal component of the pituitary LANT may have contained small, immature neuroendocrine vesicles. This result suggests that the diffuse distribution of tumour cells with a neurosecretory phenotype in our case is consistent with the features of the first reported LANT. In addition, other research facility reported that a significantly elevated serum chromogranin A level was detected in 2 of 12 patients with uterine leiomyoma, although these authors did not provide any histologic observations [13].

Recent report shown that a group of neuroendocrine neoplasms represented florid vascular proliferation resulting from angiogenic factors produced by the neoplastic cells themselves [14]. Different from this type of florid vascular proliferation, the vascular component of our case consisted of endothelial cells and vasculature-related smooth muscle cells with neurosecretory features. We proposes that uterine LANT-like tumour may be derived from neurosecretory cells that differentiated into smooth muscle cells in an angiogenic microenvironment. At present, the nature of a putative neurosecretory cell with the potential to differentiate into smooth muscle cells is unclearly understood. However, our finding of TGF-β-positive endothelial cells in uterine LANT-like tumour tissue offers support for this differentiation hypothesis because this molecule is crucial for vascular smooth muscle cell differentiation as well as cell proliferation during tumour angiogenesis [2,3]. Physiological significances of CALPONIN h1 and PSMB9/b1i in sarcomagenesis of uterine leiomyosarcoma is reportedly demonstrated by our research findings. Our research findings show possibility that both factors, CALPONIN h1 and PSMB9/b1i are potential diagnostic biomarker to distinguish uterine LANT-like tumour from other uterine mesenchymal tumours as well as uterine leiomyosarcoma [15,16,17].

In summary, we report a uterine LANT-like malignant tumour arising in myometrium. Findings for this case suggest possibility that LANT is not organ specific and may instead be a type of soft tissue tumour composed of neuroendocrine cells with the potential to differentiate into a leiomyomatous phenotype in a TGF-β-dependent manner. To confirm this hypothesis, additional examinations should be performed via immunophenotypic analysis.

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