CASE REPORT

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Leiomyosarcoma FNCLCC G3 pT2B of broad ligament adherent to right oviduct – case report with molecular profiling

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Abstract

Here we present a report of 61-year-old female patient. Uterus with left appendages was removed together with clinically tagged "tumor of right ovary" and then extensively sampled and routinely processed with Hematoxylin–Eosin (HE) and some additional staining. There was discernible oviduct adherent to grayish, solid, polycyclic 22 cm in diameter focally necrotic tumor to be diagnosed high-grade conventional leiomyosarcoma FNCLCC (*Fédération Nationale des Centres de Lutte Contre le Cancer*) G3 pT2b, according to 7th edition pTNM, according to *World Health Organization* (WHO) 2013 *International Classification of Diseases for Oncology* (ICD-O): 8890/3, in nearby of right oviduct. Grade of differentiation was given according to FNCLCC classification: grade 3 {point score: 6 = 1 [microscopically necrosis comprised 10% of the tumor] + 3 [high mitotic index eight mitoses/one high-power field (HPF) in hot spots in HE slides; Ki67 labeled approximately 60% of tumor cells] + 2 [histopathological type: conventional leiomyosarcoma]}. The staging was more appropriate for pT2b (7th edition pTNM) for deeply seated sarcoma of soft tissues, in examined samples, there was no trace of microscopically evident ovarian texture) rather than pT1a for ovarian tumors. The tumor was alpha-smooth muscle actin (α-SMA)-positive. Detected epithelial membrane antigen (EMA) immunoreactivity indicates a possible change in mesenchymal origin. Next generation sequencing revealed tumor protein p53 (TP53) mutation C275Y (7577114 C>T). Each soft tissue malignancy should be carefully reported with appropriate choice of staging and precisely graded with internationally acknowledged classification.

Keywords: leiomyosarcoma of broad ligament, EMA immunoreactivity, mesenchymal origin, next generation sequencing, P53 mutation.

Introduction

Generally, leiomyosarcoma (LMS) is a soft tissue malignancy of unfavorable course and dismal prognosis particularly for high-grade lesions [1]. In a cohort study of representative group of 349 uterine leiomyosarcomas disease-specific survival (DSS) was 42% for five-year-long period and 27% for 10-year-long period, respectively [1]. In another one investigation of 131 adult genitourinary sarcomas (mostly high-grade lesions diagnosed as leiomyosarcomas and liposarcomas) from Memorial Sloan-Kettering Centre, median survival with metastatic disease was 1.4 years in contrast to 10.7 years survival in patients without metastatic disease [2]. Disease specific survival was 56% for five-year-long period and 42% for 10-year-long period, respectively with median survival at the level of 7.6 years in this survey [2].

To our knowledge, there are no similar studies for exclusively leiomyosarcomas of broad ligament (LBL), which would comprise comparably high number of cases. Actually, based on English-written reports of LBL their incidence is very low [3]. By March 2016, there are only 23 cases of primary LBL that were reported in the English in summary provided by Chaichian *et al.* [3]. More detailed analysis of LBL cases was given by Shah *et al.* who reported that most of the tumors were right-sided, most of them were characterized by mitotic index higher than 10 mitoses/10 HPFs (high-power fields), but a mean number of mitoses ranged from 30 to 40 per 10 HPFs in a few cases [4]. Main symptomatology of LBL included pain in pelvic region, lower abdomen or in the back, loss of appetite, fatigue, dysuria and even metrorrhagia and fever [3, 4]. Generally, management of broad ligament leiomyosarcoma follows a pattern used for uterine leiomyosarcoma [3]. Most common mode of treatment was total abdominal hysterectomy with bilateral salpingo-oophorectomy that was variably followed by chemotherapy, radiotherapy, or both of them [3, 4]. Survival was not found correlated with mitotic index and it varied widely between 30 days and up to 42 months [3–5].

Taking into account this broad scope of patients' survival in course of LBL, it is recommended to clearly define factors of potential prognostic and predictive values with profound gene profiling to get more knowledge of

LBL biology. Nowadays, it is well known that some mutations like KIT (KIT proto-oncogene receptor tyrosine kinase: V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) and PDGFRA (platelet-derived growth factor receptor alpha) are of a validated predictive significance in GISTs (gastrointestinal stromal tumors) [6]. Some serious attempts of molecular grading like quantitative evaluation of chromosomal complexity such as CINSARC (complexity index in sarcomas) were designed to hopefully provide some sort of predictive information for the patients, besides histological grading systems like *National Cancer Institute* (NCI) and the *French Federation of Cancer Centers Sarcoma Group* (FNCLCC – *Fédération Nationale des Centres de Lutte Contre le Cancer*) to note the most frequently used [7]. Actually, the criteria of Zaloudek & Norris comprise presence or absence of nuclear atypia, increased cellular density or normal cellular density of the lesion and five mitoses/10 HPFs as cutoff of mitotic index [8], while Coindre introduced three-grade system, employing mitotic figures, tumor differentiation, and necrosis widely used for extra-uterine malignancies [9].

Moreover, gene signatures are of diagnostic value as they may help favor one diagnosis over another one, especially in soft tissue malignancies. For example, MDM2 (mouse double minute 2 homolog) amplification is quite characteristic for well-differentiated and dedifferentiated liposarcomas as well as in intimal sarcomas [6]. As molecular signatures could be detected in formalin-fixed, paraffin-embedded material, they could determine risk of metastasis, response to mode of peculiar treatment, provide an information on cancer biology, as well as constitute potential targets for personalized therapy or drug resistance [7]. That is why, we aimed at next generation sequencing in a malignant tumor of peculiar immunophenotype of right broad ligament of 61-year-old female patient. The patient gave the written informal consent for all medical management procedures including diagnostic and surgical procedures. The diagnostic procedures covered histopathological evaluation of slides with routine Hematoxylin–Eosin (HE) and additional immunohistochemical staining as well as next generation sequencing of panel of genes to look for any additional prognostic and predictive factors in this infrequent type of malignancy in extremely rare location at the wall of peritoneal cavity.

Case presentation

The 61-year-old woman was admitted to hospital due to discomfort in lower abdomen with flank pain. There was no history of broad ligament tumors in the relatives of the patient in heredo-collateral aspect. On clinical examination, the tumor mass was evident on palpation of abdomen. Ultrasound imaging revealed an intra-abdominal solid-appearing mass in location of right appendages. The hysterectomy with bilateral appendectomy was performed. There was a 22 cm in diameter tumor near right ovary. It was grayish, solid, polycyclic, with foci of necrosis and hemorrhage. Necrosis occupied approximately 25% of the cross-sectional area of the tumor in the macroscopic evaluation. Attached to fold of peritoneum of partially-preserved appearance of broad ligament, the tumor adhered to an elongated, narrowed right Fallopian tube of length up to 7 cm. Diagonally incised uterus measured 12×5×4 cm with macroscopically unchanged left-sided appendages. There were intramural, fibrous tumors of macroscopic appearance of leiomyomas up to 1 cm in diameter. The tissue samples were sliced and stained routinely with HE. On microscopic evaluation, there were Naboth's cysts in the cervix. Endometrium was atrophic and there were small leiomyomas with hyalinization in the uterine corpse. *Corpora albicantia* were the only findings to note in left ovary. The tumor that adhered to unchanged right ovary was conventional high-grade leiomyosarcoma FNCLCC G3 pT2b, according to 7th edition of pTNM. The ovarian tumor presented all sound features of high-grade soft tissue malignancy. The tumor was characterized architecturally by fascicular pattern of spindle plump cells (Figures 1 and 2). The lesion was hypercellular and malignant cells tended to present polymorphism (Figures 1 and 2). It was characterized with a very high dynamics of growth with mitotic index eight mitoses in one high power field (8 M/1 HPF) of the highest score in the so-called hot spots, which made the number of mitoses on average far exceeding mean 20 mitoses in 10 HPFs. Immunohistochemical evaluation confirmed it to be conventional leiomyosarcoma according to *World Health Organization* (WHO) 2013 classification [code ICD-O (*International Classification of Diseases for Oncology*): 8890/3]. It was grade 3 in estimation of the grade of differentiation in scoring of FNCLCC sarcoma classification [total points: 6 = 1 (necrosis) + 3 (mitotic activity in the study of HE) + 2 (conventional leiomyosarcoma)] [9].

Although in the studied specimens the tumor did not exceed inked its fibrous surface, there was no residue of normal ovarian tissue to state that the tumor was ovarian and that it was confined to the ovary (pT1a stage for ovarian tumors by 7th edition of pTNM). Thus, the stage of the sarcoma better fit to pT2b stage (7th edition of pTNM) for located intraperitoneally, in the abdomen, deeply localized soft tissue sarcoma: in the studied specimens. Leiomyosarcoma showed positive reaction to the EMA (Novocastra™ liquid mouse monoclonal antibody epithelial membrane antigen, product code: NCL-L-EMA, Leica Biosystems Newcastle Ltd., Balliol Business Park West Benton Lane, Newcastle Upon Tyne, United Kingdom) (Figure 3), indicating a possible change in mesenchymal origin. Thus, it could have derived from broad ligament as one of the closest anatomical structures that would correspond to its mesenchymal nature. In the differential diagnosis, fibrosarcoma was considered as a typical diagnosis of exclusion in addition to synovial sarcoma and other fusiform sarcomas. Masson's trichrome staining produced red color in hypercellular fields and bluish color in hypocellular bands of fibrosis. Alpha-smooth muscle actin (α-SMA) staining (monoclonal mouse, anti-human, anti-α-SMA clone 1A4, code M0851, Dako Denmark, Glostrup, Denmark) was strongly positive, while CD34 (Novocastra™ lyophilized mouse monoclonal anti-CD34 antibody, product code: NCL-END, clone QBEnd/10, Leica Biosystems) highlighted framework of tumor vasculature with no reactivity in tumor cells. EMA was moderately positive and MIB labeling index was high with Ki67 (monoclonal mouse anti-human, Ki67 antigen clone MIB-1, code M7240, Dako Denmark, Glostrup, Denmark) positivity in over 60% of malignant cells (Figure 2). S100 (a primary, lyophilized, rabbit,

polyclonal anti-S100 antibody, product code: NCL-S100p, Leica Biosystems, Newcastle Upon Tyne, UK) staining was inconclusive, while calretinin [Bond™ ready-to-use primary antibody calretinin (CAL6), catalog No. PA0346 Leica Biosystems Newcastle Ltd., Newcastle Upon Tyne, UK) was negative.

Along with tissue staining techniques we applied next-generation sequencing (NGS) (Ion AmpliSeq™ Cancer Hotspot Panel v2, Life Technologies, USA) to screen for structure abnormalities of following 50 genes of most often mutated oncogenes and tumor suppressors: ABL1 (Abelson murine leukemia viral oncogene homolog 1), EZH2 (enhancer of zeste homolog 2), JAK2 (Janus kinase 2), JAK3 (Janus kinase 3), PTEN (phosphatase and tensin homolog), AKT1 (serine–threonine specific protein kinase AKT–PKB), FBXW7 (F-box and WD40 repeat domain-containing 7), IDH1 (isocitrate dehydrogenase 1), IDH2 (isocitrate dehydrogenase 2), PTPN11 (tyrosine-protein phosphatase non-receptor type 11), ALK (anaplastic lymphoma kinase), FGFR1 (fibroblast growth factor receptor 1), KDR (kinase insert domain receptor), RB1 (retinoblastoma 1 gene), APC (adenomatous polyposis coli), FGFR2 (fibroblast growth factor receptor 2), KIT, RET (rearranged during transfection receptor tyrosine kinase), ATM (ataxia-telangiectasia mutated), FGFR3 (fibroblast growth factor receptor 3), KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), SMAD4 [SMAD family member 4: (MAD) from homolog of mothers against decapentaplegic and (S) from the *Caenorhabditis elegans* protein SMA (from gene sma for small body size)], BRAF (proto-oncogene B-Raf), FLT3 (Fms like tyrosine kinase 3), MET (MET proto-oncogene), SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1), CDH1 (cadherin-1), GNA11 (guanine nucleotide-binding protein subunit alpha-11), MLH1 (MutL homolog 1), SMO (smoothened, frizzled class receptor), CDKN2A (cyclin-dependent kinase inhibitor 2A), GNAS (guanine nucleotide binding protein, alpha stimulating), MPL (myeloproliferative leukemia virus oncogene), SRC (proto-oncogene tyrosine-protein kinase Src sarcoma Rous), CSF1R (colony stimulating factor 1 receptor), GNAQ [guanine nucleotide-binding protein G(q)], NOTCH1 (Notch homolog 1, translocation-associated), STK11 (serine/threonine kinase 11), CTNNB1 (catenin beta 1), HNF1A (hepatocyte nuclear factor 1 homeobox A), NPM1 (nucleophosmin1 gene), TP53 (tumor protein p53), EGFR (epidermal growth factor receptor), HRAS (GTPase HRas: transforming protein p21), NRAS (N-Ras), VHL (von Hippel-Lindau tumor suppressor), ERBB2 [receptor tyrosine-protein kinase erbB-2: proto-oncogene ERBB2 ERBB2 gene encodes HER2 (human epidermal growth factor receptor 2): HER2/neu], ERBB4 (Erb-B2 receptor tyrosine kinase 4), PDGFRA, PIK3CA (phosphatidyl-inositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha). Next generation sequencing revealed TP53 mutation C275Y (7577114 C>T) in the tumor (Table 1) (Figure 4).

Table 1 – ***Results of next generation sequencing for TP53***

Gene ID	Position	AA change	Frequency [%]	TS VC	CLC Galaxy	
TP53	7577114 C>T	C275Y	94	+	+	+

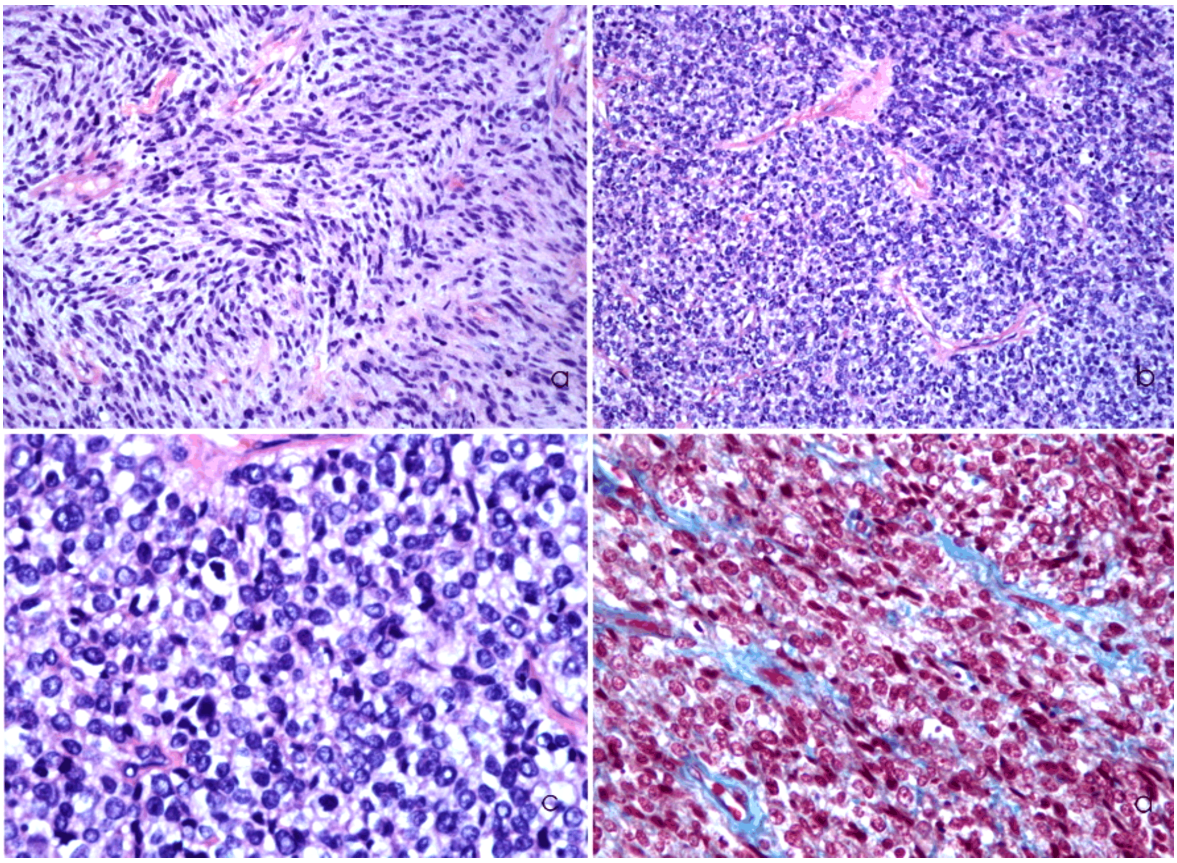

Figure 1 – ***Texture of leiomyosarcoma: (a) Fascicular pattern of leiomyosarcoma; (b) Hypercellular areas of leiomyosarcoma; (c) Highly malignant cells with polymorphism and mitotic activity (arrow); (d) Reddish staining favoring rather myogenic nature of tumor rather than fibrous one. HE staining: (a and b) ×200; (c) ×600. Masson's trichrome staining: (d) ×400.***

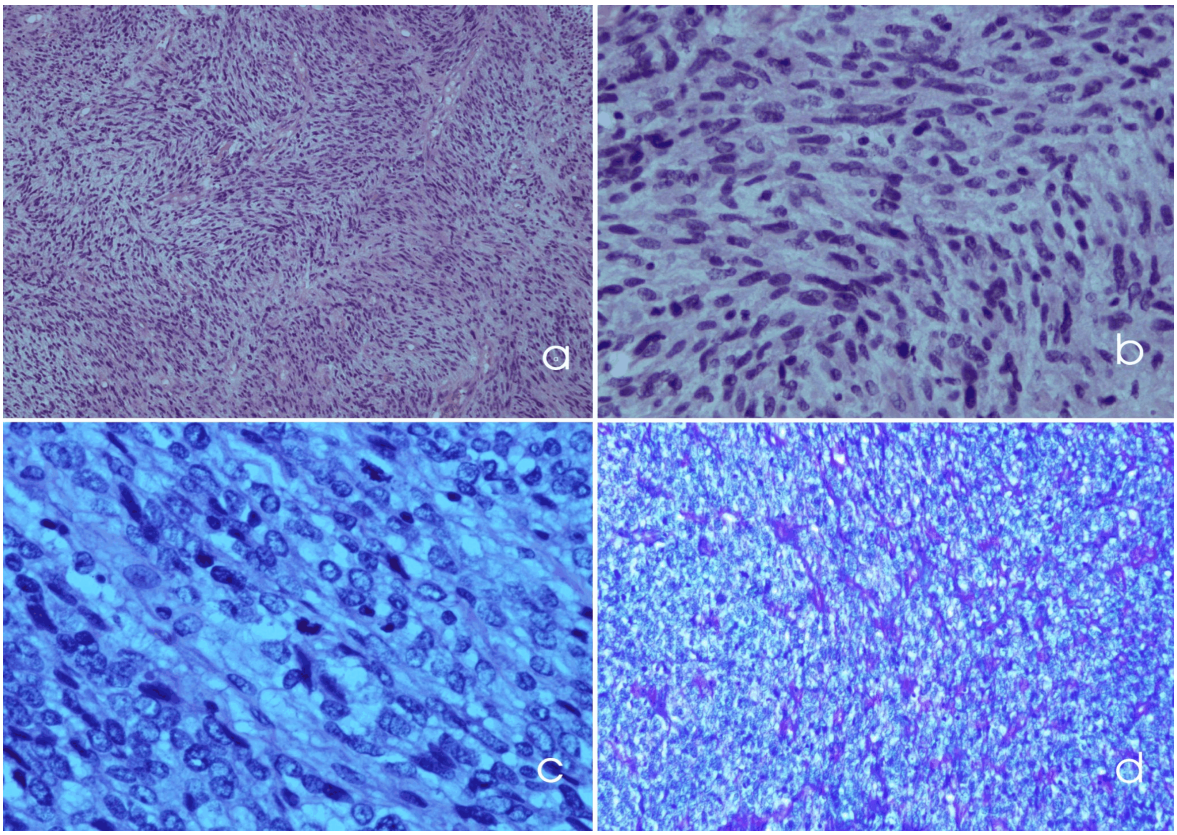

Figure 2 – ***Cytoarchitecture of leiomyosarcoma of broad ligament: (a) Low power appearance of malignant texture; (b) Fascicular streaming of sarcomatous cells; (c) Fusiform plump malignant cells with mitosis in the centre of the field; (d) Periodic acid–Schiff (PAS) reactivity is present in patched manner within the tumor while there is no hint of Alcian blue staining. HE staining: (a) ×100; (b) ×400; (c) ×600. PAS–Alcian blue staining: (d) ×200.***

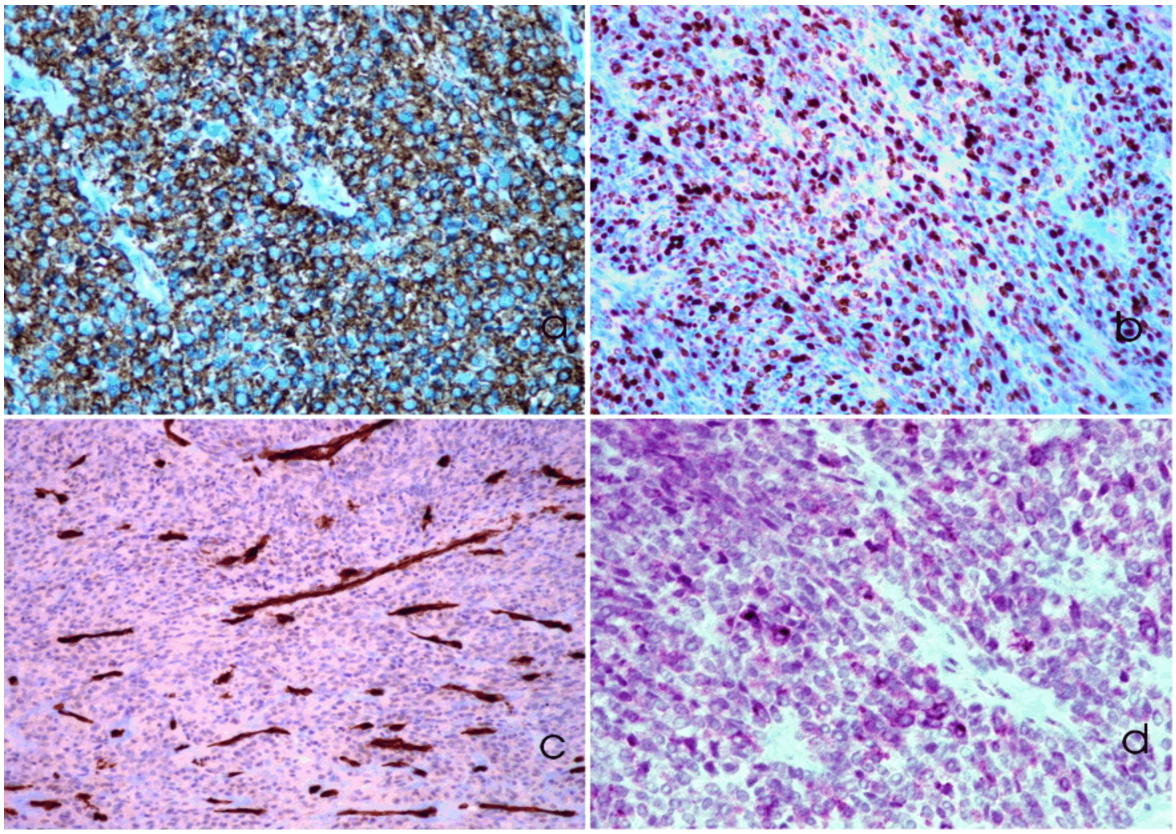

Figure 3 – ***Immunohistochemical profile of leiomyosarcoma (LMS): (a) Evident positive staining for α-SMA (×400); (b) High Ki67 MIB index in over 60% of nuclei of sarcomatous cells (×400); (c) CD34 positive staining of vascular framework inside LMS (×200); (d) EMA immunostaining distributed in membranes and cytoplasm of some malignant cells (×400).***

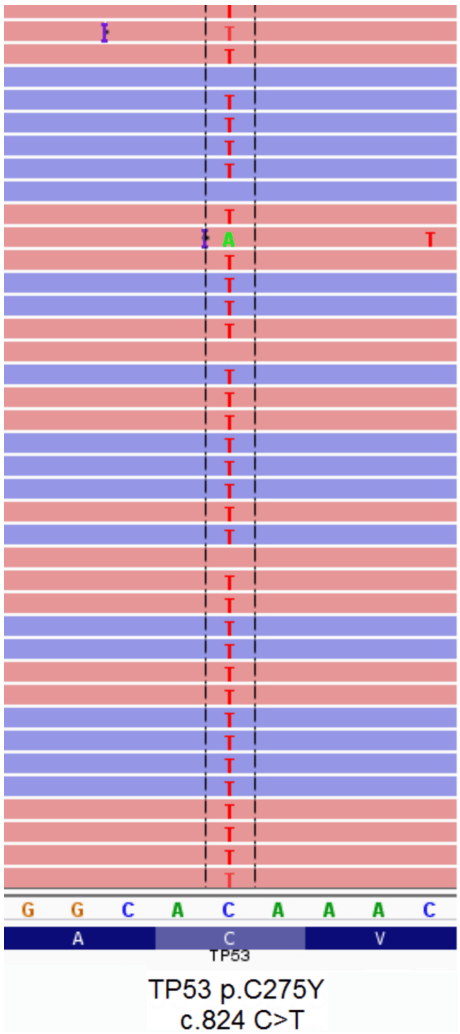

Figure 4 – ***Results of next generation sequencing for TP53.***

Discussion

Gynecological adnexal leiomyosarcomas are rare enough to merit reporting slightly over 20 reported cases so far in world literature [10, 11]. Leiomyosarcoma of the broad ligament could grow *de novo* or it rarely could be an effect of malignant transformation of a preexisting leiomyoma at this location as in case reported by Herbold *et al.* [12]. Macroscopically, primary leiomyosarcomas of the broad ligament could be partially multiple cystic in addition to solid areas while in our case it was predominantly of solid nature [11]. They were usually diagnosed at advanced stage in postmenopausal women with hepatic metastases [10]. Leiomyosarcomas are usually associated with ominous prognosis and shorter survival [10, 13, 14]. That is why genetic alterations of leiomyosarcoma are of such a great clinical concern [13]. In one study including 54 leiomyosarcomas, TP53 mutations were found in up to 35% and ATRX (ATP-dependent helicase ATRX, X-linked helicase II ATP-dependent chromatin remodeling X-linked helicase) mutations in up to 17% of studied tumors [13]. Characteristically, TP53-mutated leiomyosarcomas were found in women in uterine corpse or retroperitoneal location, while ATRX mutations were molecular signatures of fatal prognosis, as they were associated with the lengthening of telomere, poor differentiation of leiomyosarcomas and tumor necrosis [13].

Currently, molecular classification of patients with high-grade sarcoma opens a perspective to targeted therapy particularly in the light of experimental studies on mice, which harbored PTEN and TP53 mutations and developed high-grade sarcomas including leiomyosarcomas, whose aggressiveness was found to be limited by γ-secretase inhibitor that impaired Notch signaling [15].

Besides TP53, p16 an anther cell cycle regulator was found to be involved in sarcomatogenesis of female reproductive tract with noted overexpression of both regulators in carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma (ESS) [16]. Indeed, leiomyosarcomas present with substantially high rate of TP53 mutations and PTEN deletions in comparison to other histopathological types of smooth muscle tumors of female reproductive tract [17].

Due to its proximity to ovary or growth that replaces histological structure of ovary, leiomyosarcoma of broad ligament could be clinically misinterpreted as ovarian cancer as in case of 55-year-old postmenopausal woman [18].

A kind of a bit confusing immunohistochemical differential feature is EMA positivity of leiomyosarcoma, but it should be kept in mind that EMA was detected in 20 of 33 leimyosarcomas in one study, besides less frequent cytokeratin positivity, so – concerning differential diagnosis – presence of these markers is not exclusive for carcinomas, synovial sarcoma, or epithelioid sarcoma [19].

Leiomyosarcoma of the broad ligament usually grows as solitary neoplasm until giving metastases. Infrequently, it could contain rhabdoid and osteoclast-like giant cell texture as in reported case of a 38-year-old female with dynamic and fatal tumor progression [20]. In case of primary leiomyosarcoma of the broad ligament (LBL), complete surgical removal is a standard recommendation within adjuvant chemotherapy or radiation to succeed in disease-free survival with no metastasis in 15 months of follow-up period [21]. LBL usually undergoes rapid progression [21]. Thus, total abdominal hysterectomy and bilateral salpingo-oophorectomy is recognized as a standard treatment, particularly in high-grade tumors [22]. However, if leiomyosarcoma of the broad ligament is of low grade of malignancy, the patients are not administered either radiotherapy or chemotherapy, low-grade leiomyosarcoma of the broad ligament should be treated only with surgery [22]. Leiomyosarcoma of the broad ligament could metastasize virtually to every organ of the body with predilection to abdominal organs like in case of pancreatic metastasis reported by Falconi *et al.* [23]. As in our case, primary tumor of broad ligament is clearly a mass that is distinctively separate from uterus and adnexa in Gardner's diagnostic clues [24]. However, the distinction dilemma can appear in case of wide infiltration of the tumor into adjacent structures.

In the differential diagnosis of most frequent benign neoplasms, leiomyomas are first in line but also rarely occurring myolipoma, angioleiomyoma, and solitary, fibrous tumor should be of consideration [3]. This region could be affected by rare occurrence of pleomorphic sarcoma, alveolar soft-part sarcoma, and hyalinizing

spindle-cell malignancies that also enter differential diagnosis as well endometrial stromal sarcomas, uterine carcinosarcomas, and GISTs [4].

Conclusions

Any soft tissue malignancy should be carefully reported with appropriate choice of staging and precisely graded with internationally acknowledged classification. The significance of this work is a presentation of leiomyosarcoma of rare location in vicinity of oviduct with EMA immunoreactivity that indicates a possible change in mesenchymal origin. Moreover, first time in the literature we provide next generation sequencing for set over 50 genes in such a tumor with peculiar phenotype in rare location. Such genetic profiling documents for the first time C275Y mutation of TP53 in leiomyosarcoma of broad ligament.

Conflict of interests

The authors declare that they have no conflict of interests.

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