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Primary Dedifferentiated Liposarcoma of the Omentum A Case Report

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Abstract

Introduction

Soft tissue sarcomas (STSs) constitute an extensive group of aggressive and rare tumors with heterogeneous histology. Liposarcoma is the most common subtype of all soft tissue sarcomas.

Primary liposarcoma of the omentum is rare, with only 26 cases described in the literature. We report the case of a dedifferentiated liposarcoma of the omentum in a 39-year-old woman along with a literature review.

Presentation of the Case

A 39-year-old female patient was found to have an 8-cm pelvic extraovarian lesion (suspected GIST) via computed tomography, which gradually increased in size on subsequent imaging. The patient then underwent surgical resection of a 15x12x10 cm gray–white mass arising from the omentum. Pathology was consistent with a primary dedifferentiated liposarcoma of the omentum. The patient experienced recurrence 4 months after initial resection; thus, she received palliative chemotherapy.

Discussion

Primary liposarcoma of the omentum is rarely described in the literature, and its differentiation from other tumors on microscopic examination is truly challenging. Adjuvant therapy is controversial, and radical resection remains the mainstay treatment. Our patient underwent surgical resection, followed by recurrence and systemic chemotherapy.

Conclusion

The diagnosis of primary liposarcoma of the omentum is puzzling, and treatment options are not well established. Emerging data and ongoing trials raise the hope for these patients to reach an unmet need.

Keywords: Omental Liposarcoma, Omental Tumor, Dedifferentiated Liposarcoma

1. Presentation of the Case

We report the case of a 39-year-old woman who was nulligravid, had no previous medical history, and was found to have multiple uterine fibroids incidentally found via pelvic ultrasound during a routine gynecological check-up. A pelvic MRI revealed several myomatous, anterior and posterior intramural lesions, the largest of which were 18, 12 and 10 mm long, respectively. An extraovarian lesion of 60x52 mm was also found with no clear origin, requiring histopathological verification. (GIST?) A second MRI scan revealed that this mass was related to a 5x5.8 cm pedunculated subserosal uterine fibroid arising from the fundus of the uterus; thus, no resection was initially performed. The patient was still completely asymptomatic. However, a follow-up CT scan performed a few months later revealed an increase in the size of the pelvic mass, reaching 8x8.2x7 cm. On the basis of size progression, surgical exploration and resection of the tumor were then performed. A 15x12x10 cm gray–white mass with an irregular bosselated shape arising from the omentum was resected. Sectioning revealed a heterogeneous brown–white cut surface and multiple foci of hemorrhage/necrosis. The primary pathology report excluded the possibility of either leiomyosarcoma or GIST. Peritoneal washing was negative for carcinoma. The right ovary showed an endometrioma, and uterus myomectomy revealed a leiomyoma. Soft tissue synovial sarcoma was the most favorable diagnosis. Molecular profiling (FoundationONE) revealed microsatellite stability (MSS), low tumor mutational burden (2 Muts/Mb),

amplification of CDK4 and MDM2 and alteration of NF2 in Y144.

A PET CT scan 2 weeks following the surgery revealed no evidence of residual disease. An expert pathology review described a highly cellular specimen, cytologically malignant spindle cell neoplasm with a mainly fascicular growth pattern. The tumor cells had atypical hyperchromatic nuclei and amphophilic cytoplasm, with a high mitotic rate in areas with necrosis. H&E findings resembled those of MPNSTs (malignant peripheral nerve sheath tumors), but owing to their anatomic location, the possibility of dedifferentiated liposarcoma increased. In this context, immunostains for the S100 protein, EMA, TLE3, desmin, caldesmon and HMGA2 were negative, whereas there was strong multifocal nuclear positivity for MDM2 and diffuse nuclear positivity for CDK4, which is consistent with amplification of the latter genes on the long arm of chromosome 12. H3K27me3 staining was positive, i.e., normal/retained. Thus, the tumor was labeled high-grade spindle cell sarcoma, which is most consistent with dedifferentiated liposarcoma. As adjuvant chemotherapy in these cases is controversial and its role remains to be defined, decisions have been made to keep the patient under observation. MRI of the abdomen and pelvis repeated 6 months after surgery revealed numerous new metastatic lesions in both hepatic lobes and in the pelvis and lower abdomen (at least 10), as well as bilateral enlarged external iliac lymph nodes consistent with relapsed metastatic disease. As a result, the patient was started on chemotherapy and received a total of 6 cycles of adriamycin and ifosfamide. Disease evaluation after the third cycle by abdominal and pelvic MRI on September 16, 2019, revealed a partial response to treatment, with 6 liver lesions decreasing in size and the disappearance of iliac and retroperitoneal lymph nodes and a decrease in the size of the pelvic mass. A CT scan of the chest was negative. MRI of the abdomen and pelvis after 6 cycles of chemotherapy revealed partial regression of the liver lesions, with the largest measuring 12*10 mm in size compared with 22*20 mm in size, with a decrease in the size of the pelvic tumors. A partial response was also confirmed by a PET CT scan.

However, despite the favorable response to treatment, adriamycin was stopped because of cardiac toxicity; thus, the patient treatment was switched to trabectedin. After the 4th cycle of trabectidin, a pet CT scan showed an overall favorable response at the level of the pelvic and hepatic metastatic lesions, with a slight increase in activity but not in the size of the right lower pelvic soft tissue deposit. A decision to continue the same treatment was made. After 6 more cycles, a Pet CT scan revealed multiple new FDG-avid hepatic metastatic lesions and marked worsening of the peritoneal deposits, consistent with disease progression. Gemcitabine and then eribulin had no effect, as she rapidly progressed with ascites and enlarged recurrent masses in the abdomen and pelvis. Owing to her clinical and radiological deterioration, the patient sought medical advice at a different center and was lost to follow-up.

2. Discussion

Soft tissue sarcomas constitute a broad spectrum of heterogeneous diseases, with more than 100 histopathological subclasses. With a 20% incidence rate of all STSs, liposarcomas are second in classification, with the retroperitoneum and extremities being the most common sites of occurrence. Further classification is performed by the WHO according to the following histologic subtypes: well-differentiated/dedifferentiated liposarcoma (WDL/DDL), myxoid/round cell liposarcoma (MRCL) and pleomorphic liposarcoma (PLS) [1]. Compared with low-grade, well-differentiated liposarcomas, dedifferentiated liposarcomas have a worse prognosis. These patients have a greater risk for local recurrence or metastasis, with a 5-year disease-free survival rate of 16.9%, whereas the 5-year disease-free survival rate is 65.7% for low-grade liposarcoma (P<0.001), with a sixfold greater risk of death [2,3]. The 5-year overall survival rate is also worse (47.8% vs. 83.5%) [3]. Primary liposarcoma of the omentum is rarely described in the literature, with only 26 reported cases in the literature. Hashimoto et al. reported 19 cases of omental liposarcoma from 1963 until 2018, whereas Miwa et al [4]. published ultrasonographic findings in omental liposarcoma, adding 5 more cases [5]. Most recently, Atram et al. published the case of a 61-year-old woman who presented with a pelvic mass mimicking ovarian cancer and was found to have a 25.5 × 23.5 × 21 cm DDLPS with intraperitoneal metastasis [6].

The demographic review revealed an average age of 51 years, with a male predominance and various symptoms. While our patient underwent routine screening and was completely asymptomatic, the patients in the aforementioned reports presented with different symptoms, including vague abdominal pain, constipation, small bowel obstruction and abdominal distention mimicking ovarian tumors [7-11]. Tumor resection was the mainstay treatment in almost all the reported cases plus or minus adjuvant chemotherapy, mainly doxorubicin, cisplatin, and radiotherapy [11-14]. Our present patient had recurrent metastatic disease after complete resection, with the failure of 3 different lines of chemotherapy (trabectedin, gemcitabine and eribulin) after the initial treatment (ifosfamide and doxorubicin) had to be stopped owing to cardiac toxicity.

The role of chemotherapy in the treatment of sarcomas is not clearly defined. The rarity of this disease and the lack of adequate assessment make it harder to choose an optimal regimen in subsequent lines. Lehnhardt et al. studied the sensitivity of soft tissue sarcomas to 7 different chemotherapeutic agents, as single agents, as well as 4 different combinations, concluding that each histological subtype reacts differently, keeping Actinomycin D and Doxorubicin, each alone or in combination with ifosfamide as the most active agents. These results are not yet associated with clinical data from long-term follow-up observations [15]. For radiation therapy, although one study suggested improved outcomes in patients with retroperitoneal sarcoma with subtypes other than well-differentiated tumors, the use of adjuvant radiotherapy remains controversial because of

the scarcity of the disease and the associated risk of enteritis [12].

"Tumor genotyping" is on the rise, providing hope for improved adjuvant therapeutic choices and better prognoses for these patients. Dufresne et al. provided a well-directed discussion on the molecular signatures of these rare tumors and how to use personalized targeted therapy [16]. MDM2 is universally amplified in almost all WDL/DDL cases, including ours, and thus, the use of its antagonist (RG7112) might open doors to new promising active agents [17,18]. In fact, preclinical data revealed that the use of an MDM2 antagonist increased p53 levels and decreased ki67 levels (cell proliferation), leading to a partial response in 1 patient and stable disease in 14 others [19]. Similarly, Somaiah et al. described a phase I trial in which 8 patients received an MDM2 inhibitor, with a median time to progression of 23 months. Seven out of 8 patients had stable disease [25]. New-generation MDM2 inhibitors have demonstrated enhanced selectivity and perhaps superior tumor-inhibiting effects. [20,21]

The MANTRA study enrolled 160 patients with DDLPS who experienced disease progression after receiving ≥ 1 line of systemic therapy (or at least one line of treatment that included doxorubicin). The primary endpoint was PFS, which was compared between Milademetan and trabectedin. In the phase I trial, milademetan resulted in a 58.5% disease control rate and a 7.2-month PFS [22]. A phase 3 study is ongoing. In addition, another ongoing trial, Brightline-1, is evaluating the use of Brigimadlin, an oral MDM2-p53 antagonist, over doxorubicin as a first-line treatment in patients with advanced or metastatic DDLPS, with PFS being the primary endpoint [23].

Moreover, CDK4 is amplified in almost 90% of liposarcoma cases; therefore, trials are ongoing to target CDK4 [18,24]. Dickson et al. published a phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma: at 12 weeks, progression-free survival was 66%, with a median PFS of 18 weeks, which is favorable for patients who have progressive disease despite systemic therapy [26]. Another phase II trial by Dickson et al. published in 2016 demonstrated that treatment with palbociclib was actually associated with favorable PFS and occasional tumor regression [27]. Similarly, abemaciclib showed a favorable response in a phase II trial in which patients with DDLPS treated with that agent had a 76% 12-week PFS rate and a median PFS of approximately 30 weeks [28]. On the basis of these promising data, a phase III randomized, double-blind study was recently conducted in which abemaciclib was compared with placebo in patients with recurrent metastatic dedifferentiated liposarcoma [29].

3. Conclusion

Primary liposarcoma of the greater omentum is uncommon, making its differentiation from other omental tumors very challenging. Resection remains the mainstay treatment with no well-established adjuvant chemotherapy, rendering the treatment of metastatic disease even more challenging, with low response rates and dismal prognoses. Emerging data with the rapid expansion of gene sequencing and ongoing trials targeting different therapeutic pathways raise hopes for better personalized targeted therapy and possibly better outcomes for patients with advanced disease.

Availability of Data and Materials

case report no raw data

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