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Immunohistochemistry Assay for Differentiating Liposarcoma and Its Mimickers

Fira Soraya & Willy Sandhika*

Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Indonesia

E-mail: fira.soraya20@fk.unair.ac.id; willysand@fk.unair.ac.id

*Corresponding author details: Willy Sandhika; willysand@fk.unair.ac.id

ABSTRACT

Introduction: Soft tissue tumors account for 1 - 1.5% of all cancer, which is the tenth most common cancer in referral oncology hospitals in Indonesia. Liposarcomas are a group of histologically diverse lesions, accounting for 12.8% - 20% of all soft tissue malignancies. Some soft tissue tumors may show similar histological appearance, making differentiating mesenchymal neoplasms a difficult challenge. Immunohistochemical examination is an advanced examination to refine and determine the diagnosis that cannot be established based on histopathological examination only. ***Methods:*** This study was an observational descriptive study with a retrospective approach. The data of patients with liposarcoma was obtained from immunohistochemistry examination results in Dr. Soetomo General Academic Hospital during 2020 – 2022 period, which includes the histopathology result. All cases were classified based on WHO. We considered only patients with immunohistochemistry examination proven diagnosis who underwent surgery or biopsy in the same institution. ***Results:*** The total number of liposarcoma cases was 20, with most patients were male (90%) and age group 40 – 49 years old (30%). The most common location was the abdominal region (55%), including intra-abdominal, mesentery, and retroperitoneal. The most common subtype was dedifferentiated liposarcoma with 10 cases (50%). ***Conclusions:*** Immunohistochemistry examination in malignant adipocytic tumors aims to confirm the diagnosis, with the most common subtype being dedifferentiated liposarcoma. It is necessary to consider the morphology in H&E staining together with the immunohistochemistry profile as well as all clinical and radiology information to establish the most relevant diagnosis.

Keywords: tumor; neoplasm; soft tissue tumors; cancer; liposarcoma

INTRODUCTION

Soft tissue tumors account for 1 - 1.5% of all cancer [1], with the incidence is 6 / 100,000 people [2]. Soft tissue sarcoma is the tenth most common cancer in referral oncology hospitals in Indonesia [3]. The incidence of soft tissue sarcoma associated with gender, age, and location varies among histology subtypes [2, 4]. There are more than 100 different mesenchymal neoplasms, including 40 different types of soft tissue sarcoma [1]. Immunohistochemistry has an important role in the diagnosis of soft tissue sarcoma, especially when the diagnosis cannot be made based on morphology in H&E staining only due to the similar morphology [5]. Soft tissue sarcoma in some cases will express specific antigens, but in most cases, a panel of antibodies is needed because most of the antibodies used in the diagnosis of soft tissue sarcoma are non-specific [6].

Liposarcomas are a group of histologically diverse lesions that range from locally aggressive well-differentiated liposarcoma to highly malignant pleomorphic, myxoid, and dedifferentiated liposarcomas [7]. Accounting for 12.8% - 20% of all soft tissue malignancies, liposarcoma (LPS) is a commonly diagnosed sarcoma in adults [8, 9]. It is uncommon before the age of 20, but common in adults and the elderly [10]. The updated World Health Organization (WHO) classification of soft tissue and bone tumors has been recently updated with five main subtypes of liposarcoma (i) atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) (which includes lipoma-like, inflammatory and sclerosing variants); (ii) dedifferentiated liposarcoma (DDLPS); (iii) myxoid liposarcoma; (iv) pleomorphic liposarcoma (which includes epithelioid variant); and (v) myxoid pleomorphic liposarcoma [1].

The purpose of this study was to provide the immunohistochemistry profile of liposarcoma with a glimpse of its morphology on H&E staining and its mimickers.

METHODS

This study was an observational descriptive study with a retrospective approach. The data of patients with liposarcoma was obtained from the immunohistochemistry examination results of Dr. Soetomo General Academic Hospital during 2020 – 2022 period. We then retraced the previous histopathology examination result.

All cases were classified based on WHO. We considered only patients with immunohistochemistry examination proven diagnosis who underwent surgery or biopsy in the same institution as inclusion criteria. All cases that fulfill the inclusion criteria were included in this study (total sampling).

RESULTS

The total number of patients with immunohistochemistry diagnosis of liposarcoma during 2020 – 2022 period was 20. Sex distribution in this study revealed 18 patients were male and 2 were female (9:1). The youngest patient was 4 years old, while the oldest was 84 years old. 40 – 49 years was the most common age group (Table 1).

The most common location of liposarcoma in this study was in the abdominal region, consisting of intra-abdomen, mesentery, and retroperitoneal, followed by lower extremities (Table 2).

Most liposarcoma subtype in this study was dedifferentiated liposarcoma (DDLPS) with 10 cases, followed by myxoid liposarcoma and pleomorphic liposarcoma with 4 cases. All the antibodies used in immunohistochemistry examination are stated below (Table 3).

TABLE 1: Patient characteristics.

Variable	N
Sex	
Male	18 (90%)
Female	2 (10%)
Total	20
Age	
<30 years old	1 (5%)
30-39 years old	1 (5%)
40-49 years old	6 (30%)
50-59 years old	5 (25%)
60-69 years old	3 (15%)
70-79 years old	3 (15%)
≥80 years old	1 (5%)
Mean	53.9
Median	57.5
Total	**20**

TABLE 2: Tumor location.

Location	N
Thoracic region	1 (5%)
Abdominal region	11 (55%)
Intra-abdomen	6 (30%)
Mesentery	2 (10%)
Retroperitoneal	3 (15%)
Lower extremities	4 (20%)
Testis	1 (5%)
Gluteus	1 (5%)
Inguinal	2 (10%)
Total	**20**

TABLE 3: Liposarcoma subtype and antibodies used in immunohistochemistry.

Subtype	2020 (N)	2021 (N)	2022 (N)	Total (N)	Antibodies used in immunohistochemistry
Well-differentiated liposarcoma (WDLPS)	0	1	0	1	CDK4, MDM2, S100
Dedifferentiated liposarcoma (DDLPS)	0	7	3	10	CDK4, MDM2, S100, desmin, myogenin, EMA, SMA, caldesmon, CD68, CD117, DOG1, CK
Myxoid liposarcoma	2	1	1	4	MDM2, S100, SMA, CD117, vimentin, CK, HMB45, CD68
Pleomorphic liposarcoma	0	1	3	4	MDM2, S100, desmin, CD68, SMA, CK, vimentin, CD34, INI1, HMB45, CD117
Myxoid pleomorphic liposarcoma	0	0	1	1	S100, CD117, SMA

DISCUSSION

Liposarcoma is a malignant mesenchymal tumor that shows diffuse or partial adipocytic differentiation, ranging from mildly recurrent lesions to heavily metastatic neoplasms, depending on the subtype [11]. An atypical lipomatous tumor (ALT) and well-differentiated liposarcoma (WDLPS) as well as dedifferentiated liposarcoma (DDL) are the most common subgroups of liposarcoma (LPS), accounting for approximately 40% to 45% of cases [12, 13].

Well-differentiated Liposarcoma

In this study, from H&E examination, the tumor was already diagnosed as suggestive of well-differentiated liposarcoma, composed of mature adipocytes that had variation in cell size and nuclear atypia in fat cells and stromal spindle cells. Scattered hyperchromatic stromal spindle cells were identified within fibrous septa. We continued with MDM2, CDK4, and S100 staining for immunohistochemistry examination that showed positivity for MDM2, CDK4 and S100 (Figure 1).

Immunoreactivity for MDM2 and CDK4 can be observed in ALT/WDLPS [11]. Although MDM2, CDK4, and HMGA2 showing nuclear positivity can be used, they are not entirely specific as they can also be

observed in malignant peripheral nerve sheath tumors and myxofibrosarcomas. Non-neoplastic cells such as histiocytes/macrophages and multinucleated giant cells, which are often found in fat necrosis foci, can also be falsely positive and represent a pitfall [12-14]. MDM2 and CDK4 expressed in ALT/WDLPS are the result of chromosomal amplification in the 12q13-15 region [5]. All ALT/WDLPS are immunoreactive to MDM2 and 91% to CDK4 [15] as well as HMGA2 [5]. Almost all adipocytic tumors express S100. MDM2 and CDK4 are more commonly used as markers because they are not expressed in benign lipomas [14].

Dedifferentiated Liposarcoma

In this study, from H&E examination, several differential diagnoses had been made, such as leiomyosarcoma, rhabdomyosarcoma, gastrointestinal stromal tumor, undifferentiated pleomorphic sarcoma, synovial sarcoma, clear cell sarcoma and carcinoma poorly differentiated (Figure 2). We continued with CDK4, MDM2, S100, desmin, myogenin, EMA, SMA, caldesmon, CD68, CD117, DOG1, and CK staining for immunohistochemistry examination to exclude the differential diagnoses. Rhabdomyosarcoma would be positive for desmin and myogenin, leiomyosarcoma would be positive for SMA and caldesmon, synovial sarcoma would be positive for EMA and CK, gastrointestinal stromal tumor would be positive for DOG1 and CD117, undifferentiated pleomorphic sarcoma would be focally positive for CD68 and/or SMA, and clear cell sarcoma would be diffusely and strongly positive for S100 for all component.

The main role of immunohistochemistry in this entity is to confirm divergent differentiation and exclude other tumor types [1]. Dedifferentiated liposarcoma shows diffuse positive staining for MDM2 and CDK4 in the nuclei [1], as well as variable staining for SMA, desmin, and CD34 [Thway, 2016]. Positive staining of INI1 in the nucleus and in the heterologous component in the non-lipogenic area may indicate appropriate marker staining, such as positive staining of desmin and myogenin in rhabdomyoblastic elements. Generally, DDLPS shows negative staining for keratin and S100 [12]. Positive staining for MDM2 and CDK4 can be observed in both lipogenic and non-lipogenic components. The extension of staining appears to be more diffuse in the non-lipogenic dedifferentiated component, even stronger and more diffuse than in WDLPS [11, 14]. In distinguishing between WDL and DDL from other adipocytic neoplasms in their differential diagnosis, the use of CDK4, MDM2, and p16 in combination is more sensitive than that of either CDK4 or MDM2 alone [16]. A total of 100% of WDL and 93% of DDL express at least two of these triads of markers (CDK4, MDM2, and p16), and combining CDK4 and p16 offers a superior discriminatory capacity compared to either of these markers with MDM2 [16]. Among these markers, p16 was found to be the most sensitive and specific for detecting WDL/DDL, while MDM2 was found to be the least [17].

Myxoid Liposarcoma

In this study, from the H&E examination, several differential diagnoses were made, such as clear cell sarcoma, osteosarcoma, and the possibility of gastrointestinal stromal tumor and undifferentiated pleomorphic sarcoma (Figure 3). We continued with S100, MDM2, SMA, CD117, vimentin, CK, HMB45, and CD68 staining for immunohistochemistry examination to exclude the differential diagnoses. Clear cell sarcoma would be diffusely and strongly positive for S100 and HMB45, osteosarcoma would be positive for MDM2 but negative for S100, gastrointestinal stromal tumor would be positive for CD117 and focally positive for SMA and undifferentiated pleomorphic sarcoma would be focally positive for CD68 and/or SMA. We stained with CK to exclude the possibility of epithelial origin.

Myxoid liposarcoma is the second most common subtype of LPS [11]. Immunohistochemistry is useful in excluding other differential diagnoses [12] but plays a minor role in diagnosing this entity [1, 11, 14]. S100 staining varies, but is often positive, especially in lipoblasts or hypercellular or round cell areas [12, 14]. Keratin, CD34, SMA, and desmin were negative, and typically MDM2 and CDK4 were also negative, although focal expression may be present in some tumor cell nuclei [12].

Pleomorphic Liposarcoma

In this study, from H&E examination, several differential diagnoses had been made, such as malignant gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor, synovial sarcoma, undifferentiated pleomorphic sarcoma, fibrosarcoma and rhabdomyosarcoma (Figure 4). We continued with S100, MDM2, desmin, CD68, SMA, CK, vimentin, CD34, INI1, HMB45, and CD117 staining for immunohistochemistry examination to exclude the differential diagnoses.

Pleomorphic liposarcoma (PLPS) is a rare and aggressive subtype, accounting for only 5% of all LPS cases. It is characterized by the presence of large, atypical lipoblast cells [11]. Immunohistochemistry is not very helpful in diagnosing this entity [18]. S100 stains are positive in lipoblasts [12], while MDM2 and CDK4 stains are negative [1, 11, 12]. S100 can help to identify the presence of multivacuolated lipoblasts in areas where adipocytic differentiation tends to be focal and therefore easily missed [14, 19]. SMA, desmin, and CD34 show variable positivity expression in PLPS [18]. Epithelioid variants may show focal positive keratin [1] and focal positive EMA [12] as well as MelanA [1, 11].

Myxoid Pleomorphic Liposarcoma

In this study, from the H&E examination, the tumor already diagnosed as suggestive of myxoid pleomorphic liposarcoma showed mixed histological features on conventional myxoid liposarcoma and pleomorphic liposarcoma. We continued with immunohistochemistry examination, using S100 for the adipocytic component, and because the mass location is in the mesentery therefor used CD117 for the possibility of GIST and SMA for the possibility of smooth muscle origin (Figure 5).

Myxoid pleomorphic liposarcoma [MPL] is a rare and aggressive subtype, particularly occurring in children and adolescents with a predilection for the mediastinum but can also appear in the lower extremities, head and neck, perineum, abdomen, and back.

It does not have a specific immunophenotype [20] and does not show MDM2 amplification as in WDLPS and DDLPS [1]. Multiple studies have reported that tumor cells in MPLs are positive for S100 and negative for MDM2 and CDK4 immunostaining [21, 22].

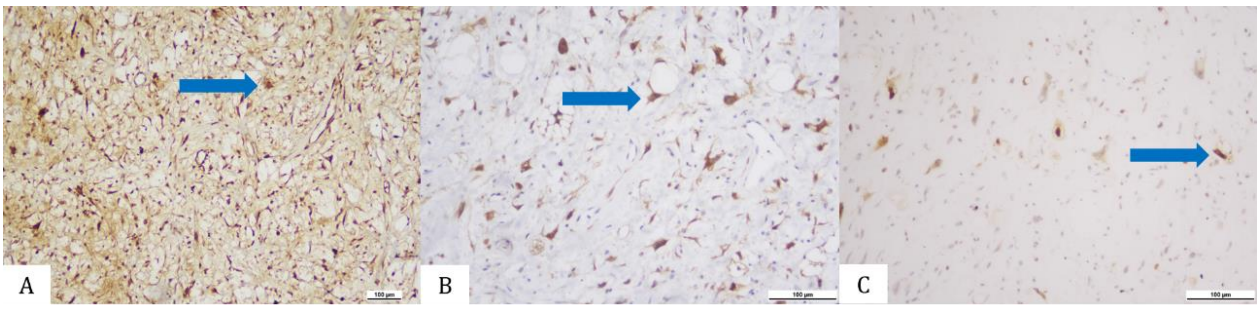

FIGURE 1: Well-differentiated liposarcoma immunohistochemistry; A. MDM2 nuclear immunopositivity was present; B. CDK4 nuclear immunopositivity was present; C. S100 immunostaining was variable.

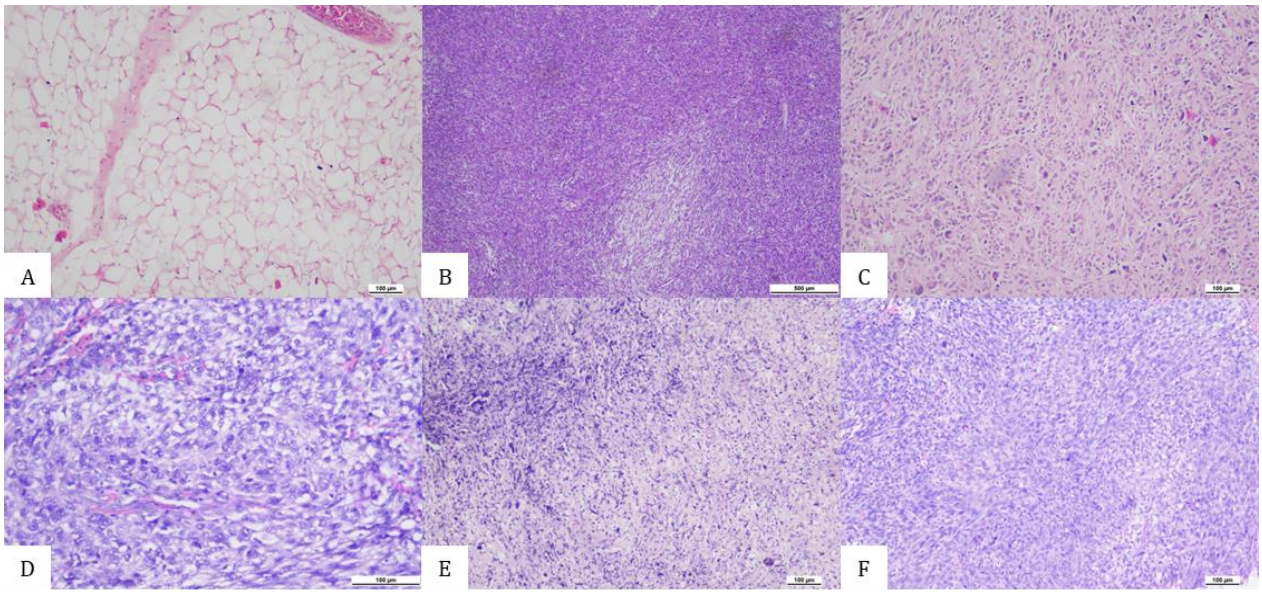

FIGURE 2: Dedifferentiated liposarcoma and its differential diagnoses; A. Well-differentiated component of liposarcoma; B. Dedifferentiated component consists of the oval to spindle cells that mimic gastrointestinal stromal tumor and leiomyosarcoma; C. Dedifferentiated component consists of oval to rhabdoid and bizarre cells with eccentric nuclei mimic synovial sarcoma and rhabdomyosarcoma; D. Dedifferentiated component consists of round to oval cells with clear to eosinophilic cytoplasm mimic clear cell sarcoma; E. Dedifferentiated components consist of severe pleomorphic cells with some of the cells have more than one nuclei and no other cells that resembles any specific type, leading to undifferentiated pleomorphic sarcoma as differential diagnosis (10x); F. Dedifferentiated component consists of round to oval cells with solid growth and clear to eosinophilic cytoplasm mimic clear cell sarcoma and carcinoma poorly differentiated.

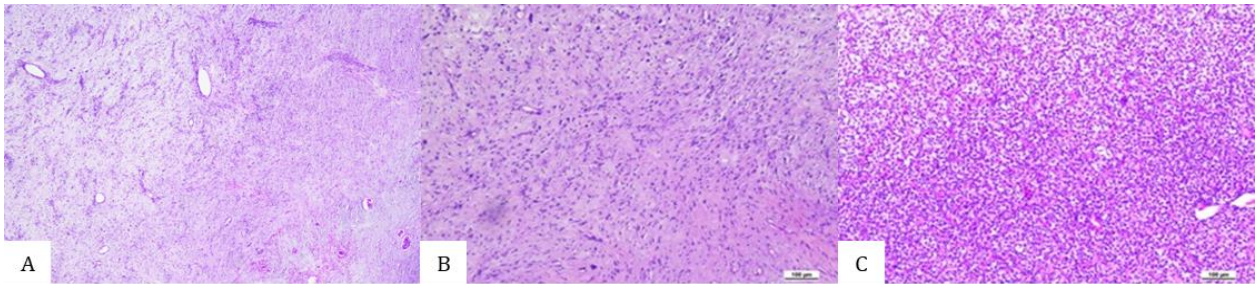

FIGURE 3: Myxoid liposarcoma and its differential diagnoses; A. tumor cells with abundant myxoid matrix and striking plexiform, delicately arborizing capillary network (chicken wire appearance) in the left area and some tumor cells between eosinophilic stroma (lace-like pattern-like) mimic osteogenic stroma in osteosarcoma in the right area; B. Tumor cells with some eccentric nuclei between eosinophilic stroma mimics lace-like pattern in osteosarcoma; C. Tumor cells with clear to eosinophilic cytoplasm mimic clear cell sarcoma.

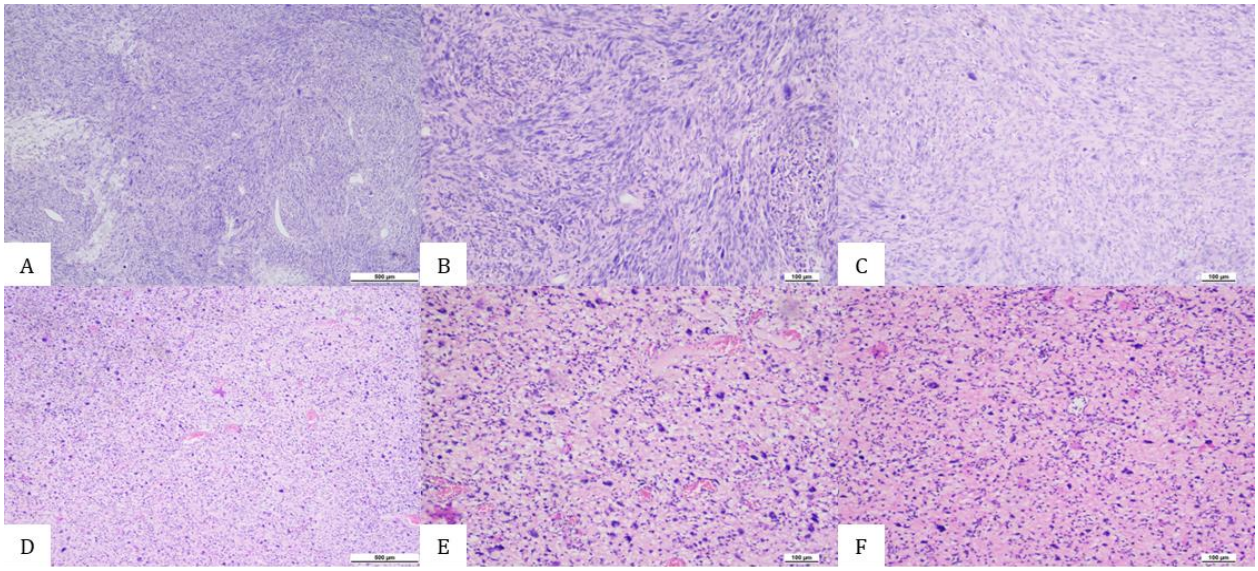

FIGURE 4: Pleomorphic liposarcoma and its differential diagnoses; A – C. Tumor cells are arranged in fascicles that intersect each other with oval–spindle nuclei and some eccentric nuclei, prominent nucleoli, and abundant mitoses. Some cells show bizarre morphology. These morphologies lead to differential diagnoses of malignant peripheral nerve sheath tumor, synovial sarcoma, undifferentiated pleomorphic sarcoma, and fibrosarcoma; D – F. Tumor cells consist of round to oval nuclei with clear to eosinophilic cytoplasm and some of spindle plump nuclei are arranged in sheets and bizarre cells with pleomorphic nuclei between them lead to differential diagnosis malignant gastrointestinal stromal tumor and liposarcoma.

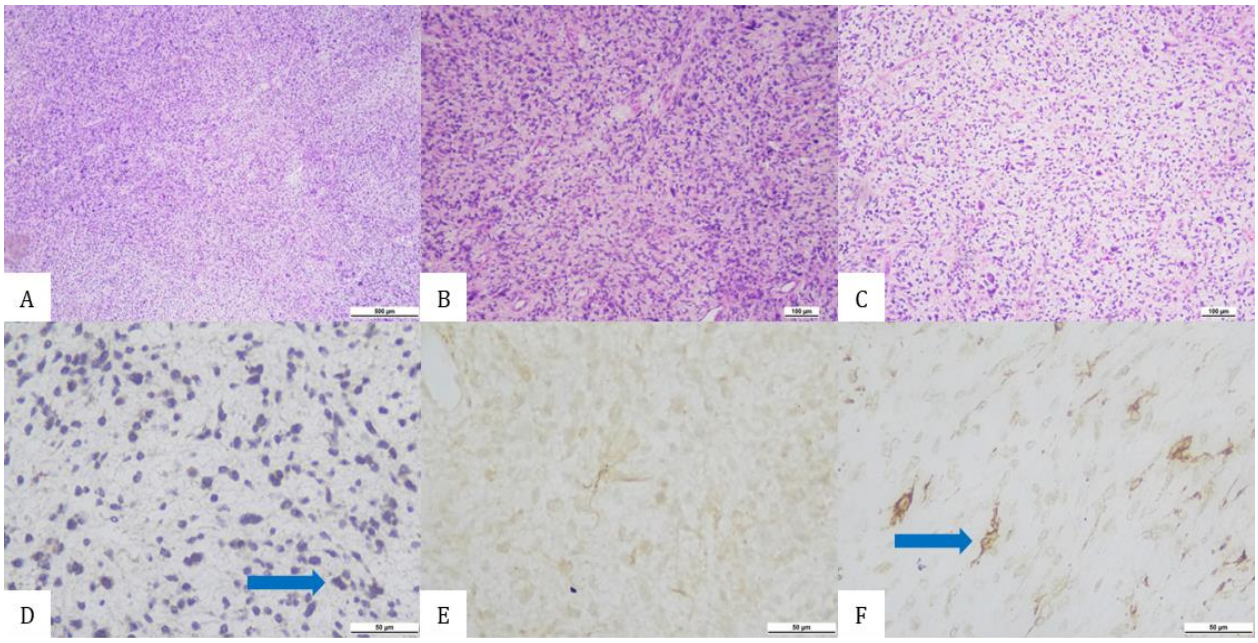

FIGURE 5: Myxoid pleomorphic liposarcoma and its differential diagnoses; A-C. Tumor cells with pleomorphic nuclei and prominent nucleoli and some of the cells show bizarre morphology and have oval to spindle nuclei. There is also myxoid stroma and a delicately arborizing capillary network (chicken wire appearance). D. S100 immunostaining was focally positive; E. CD117 immunostaining was negative; F. SMA immunostaining was focally positive.

CONCLUSIONS

Immunohistochemistry examination in malignant adipocytic tumor cases aims to confirm the diagnosis, especially in cases where the diagnosis cannot be made based on morphology in H&E staining only. To establish the most relevant diagnosis for patient management and prognosis, it is necessary to consider all clinical and radiographic examination information, as well as anatomical pathology and immunohistochemistry examination. It is important to note that none of these examinations can stand alone in tumor diagnosis.

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