International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Clivus Undifferentiated Pleomorphic Sarcoma. A Case Report

Pedro Duran[1], Christian Edward Sánchez-Sánchez[2], Eliezer Villanueva[3], Citlaltepetl Salinas-Lara[4], Carlos Sanchez-Garibay[5], Martha Lilia Tena-Suck[6*]

[1]Department of Neuropathology. National Institute of Neurology and Neurosurgery, Mexico

[2]Imagen Service. National Institute of Neurology and Neurosurgery, México

[3]Service of Neurosurgery. National Institute of Neurology and Neurosurgery, México

[4]Department of Neuropathology. National Institute of Neurology and Neurosurgery, México

[5]Department of Neuropathology. National Institute of Neurology and Neurosurgery, México

[6]Department of Neuropathology. National Institute of Neurology and Neurosurgery, México

---

Citation: Duran P, Sánchez-Sánchez CE, Villanueva E, Salinas-Lara C, Sanchez-Garibay C, Tena-Suck ML. Clivus Undifferentiated Pleomorphic Sarcoma. A Case Report. *Int Clinc Med Case Rep Jour. 2024;3(6):1-13.*

Received Date: 17 June, 2024**;** **Accepted Date:** 20 June, 2024**;** **Published Date:** 24 June, 2024

[*]**Corresponding author:** Dr. Martha Lilia Tena-Suck, Department of Neuropathology. National Institute of Neurology and Neurosurgery, México, Tel: +525556063822

ABSTRACT

Undifferentiated pleomorphic sarcoma, previously called malignant fibrous histiocytoma, is a prevalent tumor, and it is usually associated with trauma and radiotherapy. They are found anywhere in the body, but those reported with localization at the skull base are very rare. The case of a 19-year-old girl who began with headache, vertigo, dysphagia to solids and liquids, and dysphonia, with a deviation of the tongue to the right, loss of balance to the right, and incontinence of urinary sphincters, is presented. A brain computed tomography was performed, which showed a lesion in the clivus with a diagnosis of chordoma. She underwent surgery and a small tissue fragment for intraoperative

crushed study was performed and reported as a malignant neoplasia suggestive of sarcoma. In the definitive study, fibrohistiocytic neoplasia formed irregular bundles with a storiform appearance, identifying large atypical giant pleomorphic cells that show cellular inclusions. Immunohistochemistry was positive for Vimentin, alpha 1-antitrypsin, fascin, CD68, and focally in fibrillar pattern for smooth muscle actin and CD34. Based on the histological and IHC findings, an undifferentiated pleomorphic sarcoma was diagnosed. Very few cases of undifferentiated pleomorphic sarcoma in the skull base have been reported.

Keywords: Undifferentiated pleomorphic sarcoma; Malignant fibrous histiocytoma; Mesenchymal stromal or stem cells; Clivus tumors.

ABBREVIATION

MFH: Malignant Fibrous Histiocytoma

UPS: Undifferentiated Pleomorphic Sarcoma

α-SMA: Alpha-Smooth Muscle Actin

HHF-35: Muscle Specific Actin

MSC: Mesenchymal Stromal or Stem Cell

PRM: Pleomorphic Rhabdomyosarcoma

PLDL: Pleomorphic and Dedifferentiated Liposarcoma

PLMS: Pleomorphic Dedifferentiated Leiomyosarcoma

MPNST: Pleomorphic Malignant Peripheral Nerve Sheath Tumors

POGS: Pleomorphic Osteosarcoma

EMA: Epithelial Membrane Antigen

MSA: Smooth Muscle Actin

CALD: Caldesmon

OCN: Osteocalcin

COL-IV: Collagen IV

α1-antitrypcin.

INTRODUCTION

Kauffman and Stout first introduced malignant fibrous histiocytoma (MFH) in 1961. They described it as a tumor rich in histiocytes with a storiform growth pattern. By 1977, MFH was considered adult life's most common soft tissue sarcoma[1].

Malignant fibrous histiocytoma (MFH) is a neoplasm supposed to originate from primitive mesenchymal cells. 2002, the World Health Organization (WHO) declassified malignant fibrous histiocytoma as a formal diagnostic entity. They renamed it undifferentiated pleomorphic sarcoma (UPS), which fundamentally represents a diagnosis of exclusion and is classified under the undifferentiated/unclassified sarcomas group[2]. MFH has a variable histological feature and often transitions from areas with a highly ordered storiform pattern to less differentiated areas with a pleomorphic appearance[2]. These have been later reclassified as distinct entities, with the developments in cytogenetics and immunohistochemistry studies[2,3].

It has been characterized into five subtypes: (a) storiform/pleomorphic, (b) myxoid, (c) giant cell, (d) inflammatory, and (e) angiomatoid[2]. The most common histological patterns have been reported as storiform/pleomorphic, forming 50-60% of all such tumors, while the myxoid type is the second most reported at 25%[3].

Soft tissue MFH can arise in any body part, from soft tissue or bone, usually in the extremities or retroperitoneum[2]. Skull base and clivus are scarce[3-7].

UPS is the most shared soft tissue sarcoma of late adult life and is usually between 32-80 years old with a slight male predominance[2,3]. Local mass effect symptoms may be caused depending on the tumor's location. Symptoms consist of generally a painless, enlarging mass[1]. However, UPS has a high incidence of local recurrence and metastasis[2,3].

Risk factors include radiation treatment for another malignancy, such as Hodgkin’s lymphoma, post-radiotherapy, a background history of Paget’s disease, non-ossifying fibroma, and fibrous dysplasia. Soft tissue sarcoma has been related to specific syndromes, such as Werner, Gardner, Li Fraumeni, and Von Recklinghausen[2].

Immunohistochemical stains showed a positive immunoreaction for alpha-smooth muscle actin (α-SMA), muscle-specific actin (HHF-35), desmin, vimentin, and CD68, y CD34. and negative for calretinin, cytokeratin, TTF-1, CD56, LCA, CD34, and S-100 protein, bcl-2, and CD99. The expression of these markers is not specific and does not point toward evidence of a specific line of differentiation[2].

This case report aimed to describe a Clivus undifferentiated pleomorphic sarcoma not associated with radiotherapy in a young female.

CLINICAL CASE

A 19-year-old woman with no significant history, onset one year ago, with headaches that increased in intensity, three months prior onset with vertigo, dysphagia to solids and liquids, dysphonia, with deviation of the tongue to the right, and loss of balance to the right. She went to the emergency department at our institution and had a brain CT scan showing an extensive lesion of the clivus with a diagnosis of chordoma. Simple skull CT in the bone window reported an expansive lytic lesion with the destruction of the left occipital condyle with extension to the temporal petrous bone, jugular foramen, and carotid canal (Figure 1a). Sagittal STIR, T1FS+ Axial Gadolinium, and axial DWI showed a heterogeneous solid lesion predominantly hyperintense on T2 with intense enhancement, showing an area of diffusion restriction (Figures 1(b-d)). She underwent surgery, and an intraoperative study was performed and reported a malignant neoplasm that suggested sarcoma. Observing a dirty bottom with cellular debris and occasional naked cells and nuclei, with a pleomorphic appearance (Figure 2). Histologically, a sarcomatous type malignant neoplasm is observed, with a storiform-like swirling pattern, with bundles in all directions in which elongated pleomorphic hyperchromatic cells and large multinucleated cells stand out (Figure 3(a-d)). Motley cells, occasionally lymphocytes, and plasma cells are observed. The different cell bundles were intensely blue with the Masson stain (Figure 3(e,f)), and the reticular fiber stain was focally positive (Figure 3g). With the Alcian blue stain, the background was a focal positive stain (Figure 3h). Immunohistochemistry shows strong positivity for vimentin (Figure 4a), alpha 1 chymotrypsin (Figure 4b), lysozyme (Figure 4c), and CD68 (Figure 4d) focal and fibrillar smooth muscle actin (Figure 4e), fascin (Figure 3f), CD79a. Negative for MioD. Based on the histological and immunohistochemical findings, undifferentiated pleomorphic clivus sarcoma was diagnosed.

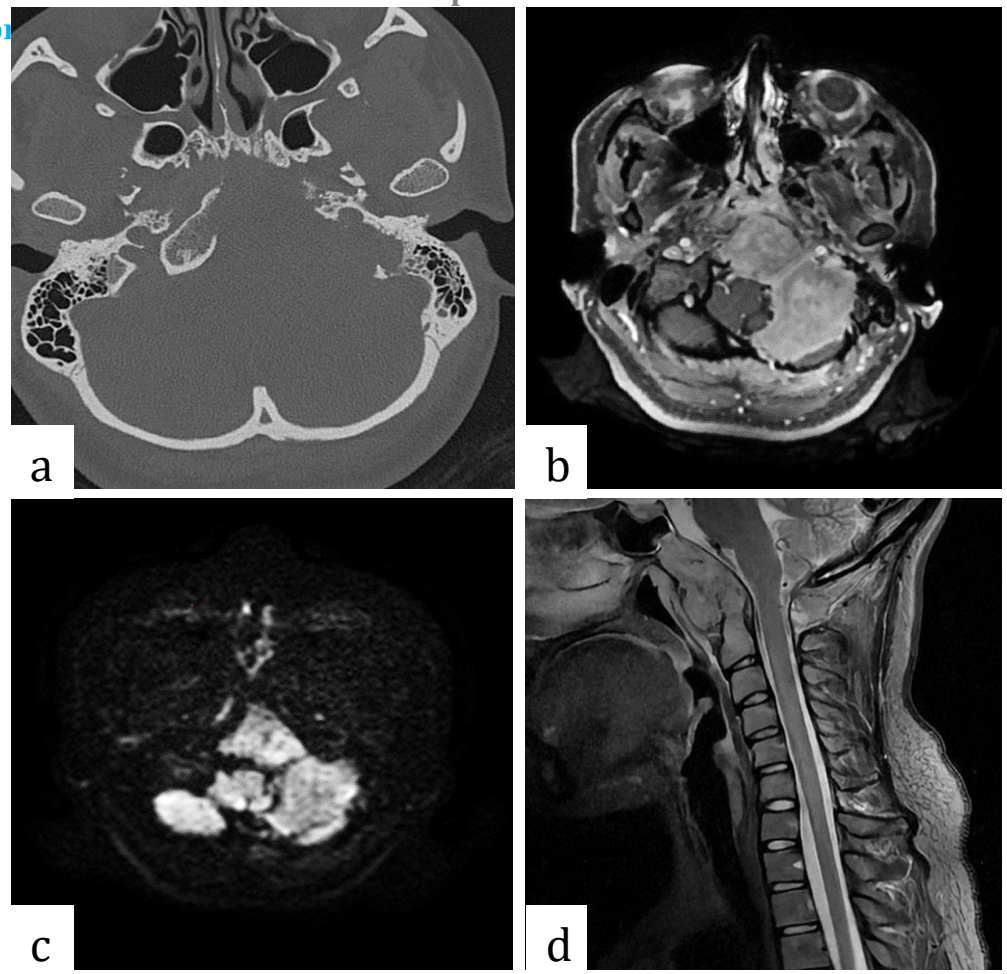

Figure 1. (a) Simple skull CT in bone window. An expansive lytic lesion with the destruction of the left occipital condyle, extension to the temporal petrous bone, jugular foramen, and carotid canal. (b) and (c) observed a heterogeneous solid lesion, predominantly hyperintense on T2 with intense enhancement, showing an area of diffusion restriction. (d) showed Sagittal STIR, T1 FS+ Axial Gadolinium, and axial DWI.

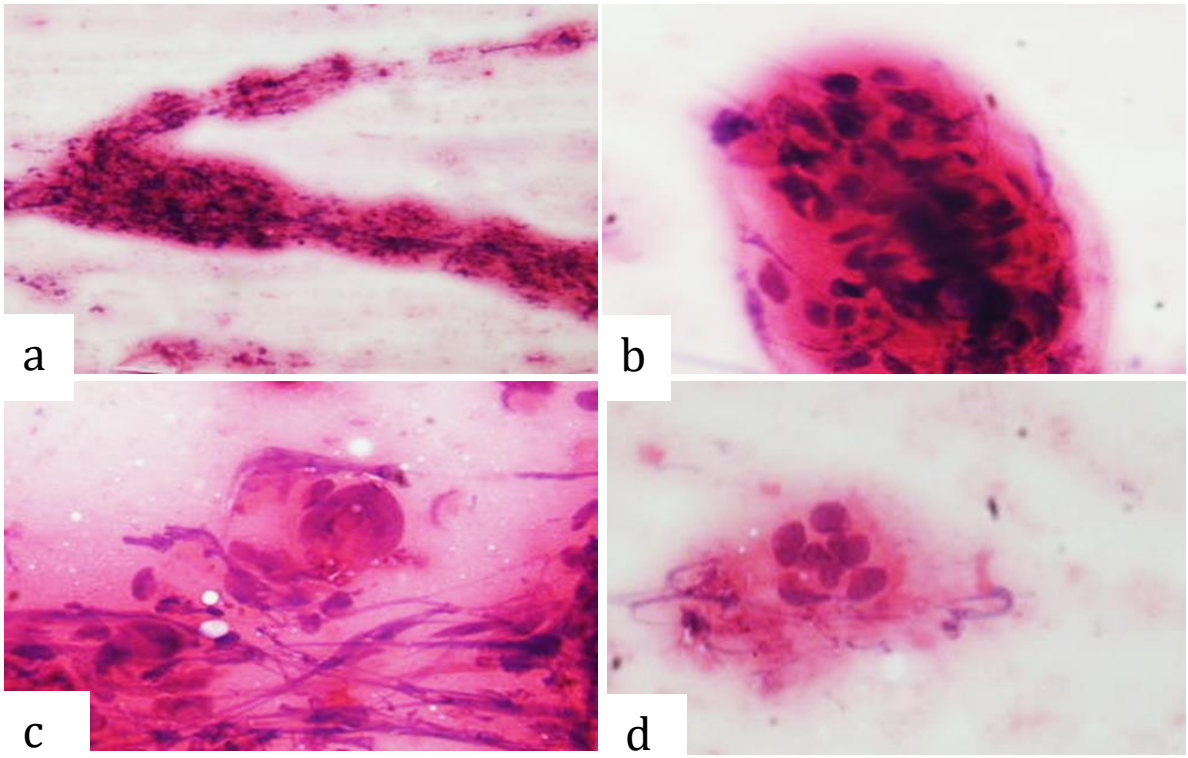

Figure 2. Transoperative Crushed study. (a) Shows a dirty smear background with abundant cellular debris that is observed in thick nests of poorly differentiated cells, some fusocelular and others small, (b) alternating with pleomorphic cells and pleomorphic cells with naked nuclei (H&Ex400), (c) and showed large multinucleated cells with osteoclastic nuclei appearance in (d) (H&E x200).

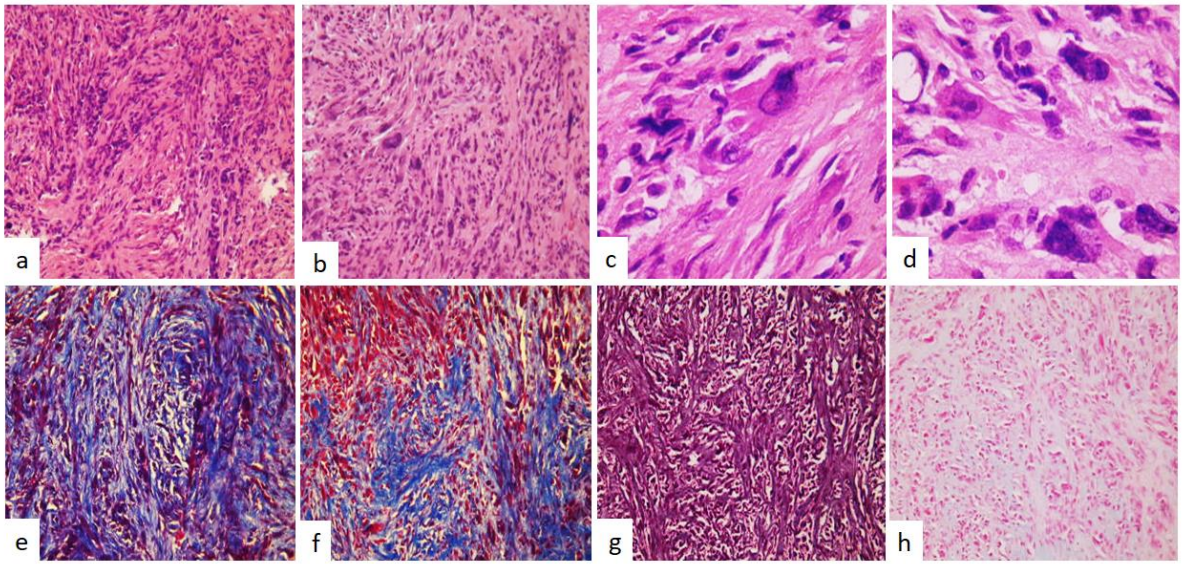

Figure 3. Histologically, the tumor is formed by (a) a malignant mesenchymal neoplasm formed by bundles of elongated cells with a storiform pattern. (b) Observed large cells of variable large sizes (H&Ex100), (c) Showed pleomorphic cells with little cytoplasm with bizarre hyperchromatic nuclei, some with inclusions, and others with marked cellular atypia in (d) (H&E x400). (e) Masson stain was intensely positive, delimiting the storiform pattern in (f) with areas of fibrosis (Masson stain x 200). (g) Reticular fibers, staining is poor (x200), and in (h), Alcian blue stain was stromal slightly positive (x200).

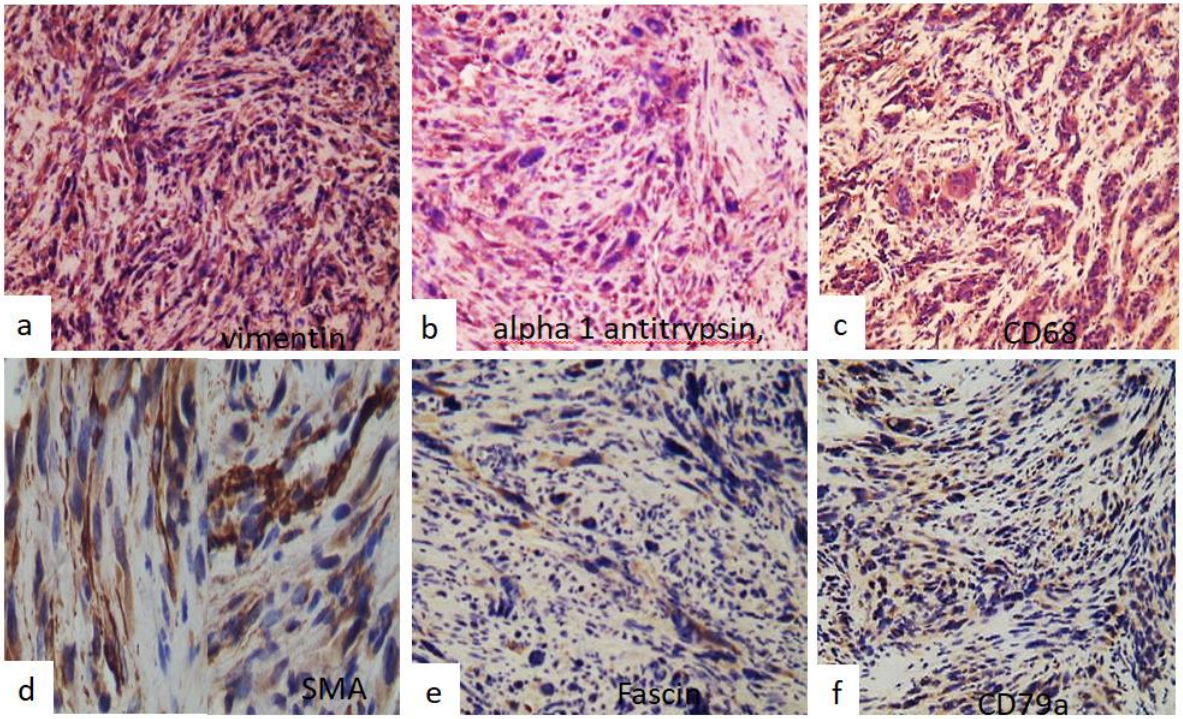

Figure 4. By immunohistochemistry, the tumor was positive for (a) vimentin, (b) alpha 1 antitrypsin, (c) CD68, (d) SMA showing focally positive cells, but positive stromal beaded fibers, weak positive immunoreaction for fascin in (e) and (f) showed CD79a weak positive immunoreaction (IHC stain x200).

DISCUSSION

UPS located at the skull base/clivus is extremely rare; only around 20 cases are described in the literature. These tumors' radiological and clinical features are nonspecific and require histopathological confirmation. MRI images show homogeneous iso- or hyperintense lesions on T1-weighted imaging and heterogeneous hypo- or hyperintense lesions on T2-weighted imaging. The principal radiological differential diagnosis was with chordoma due to the location and frequency; however, the differential diagnoses included chondrosarcoma and fibrous dysplasia[8]. The substantial contrast enhancement may resemble lymphomas, Langerhans cell histiocytosis, or intraosseous hemangiomas. The

differential diagnosis of clival lesions also includes metastases on the occipital bone, reported from prostate cancer in most outstanding cases, though those from thyroid cancer and hepatocarcinoma have been reported less often; another uncommon occurrence of tumors in the area of the clivus presentation is plasmacytomas[8].

The etiology of UPS is unknown, but some cases are supposed to originate following radiation therapy. Currently, it is considered a post-radiation neoplasm[9]; there is an estimated lifetime risk of up to 0.3%[9]. In addition, some authors have also suggested that UPS may progress from its formerly believed benign component, benign fibrous histiocytoma[2,7,8]. Although the histogenesis of this neoplasm remains debatable, it has been considered a primitive and pleomorphic sarcoma showing partial fibroblastic and histiocytic differentiation. UPS comprises heterogeneous populations of cells with mesenchymal features that can originate from simple genomic alterations or complex genomics[10]. Tumor-initiating cells characteristics with stem cells and the predecessor cell from which the tumor rises. Sarcomas, a progenitor cell type, could be a mesenchymal stromal or stem cell (MSC)[10]. Indeed, previous studies have shown that mesenchymal tumors can arise from targeting the expression of an oncogenic mutation in a mesenchymal stromal or stem cell (MSC) population[11].

Although nonspecific, genetic alterations, such as mutations, deletions, and epigenetic modifications, may be necessary for undifferentiated sarcoma development and progression[10].

UPS shows various potential cellular backgrounds, mutational signatures, and altered signaling pathways. Yes1-associated transcriptional regulator (YAP1) and TEAD transcription factors, vestigial-like family member 3 (VGLL3), PRDM10 and other cofactors are found to be highly amplified in a genome sequencing study[11]. Also, the Hedgehog signaling pathway plays a role in the proliferation and malignancy[12]. Several studies have revealed frequent MDM2, CDK4, PDFGRA, KIT amplifications, and CDKN2A and CDKN2B deletions[13]. Regularly mutated cancer driver genes, including PDGFRB, TP53, ALK, PTCH1, RET, ERBB4, JAK3, GATA1, PIK3CG, and RARA, were identified. Several new potentially actionable mutations, including those in RARA, ALK, PTCH1, RET, ROS1, ABL1, and MET, were also found[13].

Numerical and structural variants underlying chromosomal aberrations are frequently observed in undifferentiated sarcoma, indicating the critical role of high chromosomal instability in sarcomagenesis and progression. Losses of 13q12-q14 or 13q21 were observed in many tumors, suggesting that a gene localized in this region could act as a tumor suppressor gene[14].

The histological aspect of UPS suggests an aggressive spindle-cell neoplasm, and it is characterized by the presence of a wheel-like structure, showing spindle-shaped cells such as fibrocytes and histiocytes arranged in a storiform pattern. Numerous giant cells show eosinophilic cytoplasm on staining; single or multiple irregular nuclei are observed,

with inflammatory cells often mixing with the tumor cells. In the present case, spindle-shaped cells were arranged in a storiform pattern, and numerous pleomorphic cells with high mitotic rates were observed[2]. Immunohistochemistry demonstrates diffuse staining for vimentin and CD68 and only focal reactivity for desmin, SMA, fascin, CD79a, and CD34, confirming the diagnosis of UPS[15].

Histologically, the differential diagnosis covers a large number of malignant neoplasms, both due to the sarcomatous pattern and due to the pleomorphic cells, such as pleomorphic leiomyosarcomas, rhabdomyosarcomas, liposarcomas, osteosarcomas, malignant nerve sheath tumors, melanomas, lymphomas, and carcinomas, myofibroblastic sarcoma, low-grade myxofibrosarcoma, sarcomatoid carcinoma, osteogenic sarcoma[2,16]. Etc. The expression of the different markers by immunohistochemistry is shown in (Table 1).

Table 1. Showed the diagnosis differential within pleomorphic sarcomas
PRIMARY

ANTIBODY	MFH	PRMS	PLPS	PLMS	POGS	MPNST
keratin	No	Non	+	non	non	Non
EMA	No	Non	Non	+	Non	+
vimentin	++	++	++	++	++	++
desmin	+	Non	Non	++	+	++
MSA	+	+	Non	+++	Non	Non
CALD	No	Non	Non	non	Non	Non
S-100	No	Non	Non	Non	Non	+++
CD57	+	Non	Non	Non	Non	++
COL-IV	++	+	++	++	++	++
CD34	+	Non	+	Non	Non	Non

CD99	+	+	Non	non	Non	+
OCN	+	Non	Non	non	++	Non
Myo-D1	+	+++	Non	+	Non	Non
myogenin	non	+++	Non	non	No	Non
CD68	+++	Non	Non	Non	Non	Non
α1antit	+++	Non	Non	Non	Non	Non
ACTIN	No	+	Non	+	+	Non
FASCIN	+++	Non	non	non	Non	Non
GFAP	non	non	non	Non	non	+

Malignant fibrous histiocytoma (MFF), pleomorphic rhabdomyosarcoma (PRM), pleomorphic and dedifferentiated liposarcoma (PLDL), pleomorphic dedifferentiated leiomyosarcoma (PLMS), pleomorphic malignant peripheral nerve sheath tumors (MPNST), Pleomorphic osteosarcoma (POGS). Epithelial membrane, antigen (EMA), Smooth muscle actin (MSA), caldesmon (CALD), osteocalcin, (OCN), Collagen IV(COL-IV). α1-antitrypcin.

UPS represents the correct label for MFH's prototypical storiform and pleomorphic variant. Giant cell MFH is presently replaced by three distinct tumor types: giant cell tumor of soft tissues, extraskeletal osteosarcoma, and giant cell-rich osteosarcoma. Myxoid MFH is currently recognized as a purely fibroblastic tumor identified with the original name myxofibrosarcoma, called inflammatory MFH, which overlaps entirely with the inflammatory variant of dedifferentiated liposarcomas. So-called angiomatoid MFH (as a clinically indolent lesion most often harboring an EWSR1-CREB1 fusion gene and, more rarely, EWSR1-ATF1 or a FUS-ATF1), which is currently listed within the group of soft tissue lesions of unknown differentiation[17].

CONCLUSION

We present a rare case of clivus sarcoma with extensive and rapidly evolving destruction. As a young woman. Which expresses CD99, MIOD1, nestin, and CD34 in a diffuse stromal form. Finding that could be related to tumor dedifferentiation. Considering it as a mesenchymal stromal or stem cell population.

REFERENCES

1. Ozzello L, Stout AP, Murray MR. Cultural characteristics of malignant histiocytomas and fibrous xanthomas. Cancer. 1963;16:331-344.
2. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO Classification of Tumors of Soft Tissue and Bone. Pathology and genetics of tumors of soft tissue and bone 2013.
3. Chen K-H, Chou TM, Shieh SJ. Management of extremity malignant fibrous histiocytoma: a 10-year experience. Formos J Surg. 2015;48:1-9.
4. Mahore A, Ramdasi R, Dange N, Epari S. Malignant fibrous histiocytoma of the skull base: A neurosurgical nuance. Asian J Neurosurg. 2015;10(2):135-138.
5. Cook BR, Vries JK, Martinez AJ. Malignant fibrous histiocytoma of the clivus: case report. Neurosurgery. 1987; 20(4):632-635.
6. Joo M, Lee GJ, Koh YC, Kwon OK, Park YK. Primary intraosseous malignant fibrous histiocytoma of the skull: a case report. J Korean Med Sci 2003;18(4):609-613.
7. Hardison SA, Davis PL, Browne JD III. Malignant fibrous histiocytoma of the head and neck: A case series. Am J Otolaryngol 2013;34:10-15.
8. Davis JL, Tihan T, Kilpatrick SE. Mesenchymal Tumors of the Central Nervous System. In Practical Surgical Neuropathology: A Diagnostic Approach, 2nd edn. Perry A, Brat DJ. 2018;299-322.
9. Dineen SP, Roland CL, Feig R, et al. Radiation-Associated undifferentiated pleomorphic sarcoma is associated with worse clinical outcomes than sporadic lesions. Ann Surg Oncol. 2015;22(12):3913-3920.
10. Matushansky I, Hernando E, Socci ND, et al. Derivation of sarcomas from mesenchymal stem cells via inactivation of the Wnt pathway. J Clin Invest. 2007;117(11):3248-3257.
11. Wang CY, Wei Q, Han I, et al. Hedgehog and Notch signaling regulate self-renewal of undifferentiated pleomorphic sarcomas. Cancer Res. 2012;72(4):1013-22.
12. Hélias-Rodzewicz Z, Pérot G, Chibon F, et al. YAP1 and VGLL3, encoding two cofactors of TEAD transcription factors, are amplified and overexpressed in a subset of soft tissue sarcomas. Genes Chromosomes Cancer. 2010;49(12):1161-1171.
13. Cui Y, Han L, Shang J, et al. Primary cardiac undifferentiated pleomorphic sarcoma is associated with TP53 mutation during lack of MDM2 amplification, and targeted sequencing analysis reveals potentially actionable targets. Hum Pathol. 2022:123:113-122.
14. Mairal A,Terrier P, Chibon F, Sastre X, Lecesne A, Aurias A. Loss of chromosome 13 is the most frequent genomic imbalance in malignant fibrous histiocytomas. A comparative genomic hybridization analysis of a series of 30 cases. Cancer Genet Cytogenet. 1999;111(2):134-138.
15. Thway K, Fisher C. Undifferentiated and dedifferentiated soft tissue neoplasms: Immunohistochemical surrogates for differential diagnosis. Semin Diagn Pathol. 2021;38:170.
16. Sbaraglia M, Bellan E, Tos APD. The 2020 WHO Classification of Soft Tissue Tumours: News and perspectives. Pathologica. 2021;113(2):70-84.

17. Rossi S, Szuhai K, Ijszenga M. EWSR1-CREB1 and EWSR1-ATF1 fusion genes in angiomatoid fibrous histiocytoma. Clin Cancer Res. 2007;13(24):7322-7328.