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Undifferentiated Pleomorphic Sarcoma of the Conjunctiva: A Case Report and Review of the Literature

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Abstract. *Background/Aim: Undifferentiated pleomorphic sarcoma (UPS), previously called as malignant fibrous histiocytoma, is a mesenchymal neoplasm which shows no identifiable cellular differentiation when analyzed by presently available technology. UPS in the periocular region is extremely rare. This study describes a patient with UPS arising in the conjunctiva with literature review. Case Report: A 66-year-old man presented with a congested mass on the bulbar conjunctiva. The mass was totally excised. Histopathologically, it was a dome-shaped tumor comprising atypical short spindle cells growing as pattern-less pattern, with enlarged nuclei and eosinophilic cytoplasm. Based on immunohistochemistry, the direction of cellular differentiation was unidentifiable; therefore, it was diagnosed as UPS. The tumor showed high Ki-67 labeling index (70~80%). Conclusion: Twelve patients with conjunctival UPS have been reported with an average age of 49 years. Eight tumors of the 12 patients were observed in the limbus, and the rest in the bulbar conjunctiva. The appearance of the tumors was yellow, tan, pink, brown, or vascularized. Histopathologically, the tumors consisted of spindle-shaped cells with pleomorphism and many mitotic figures. In conclusion, conjunctival UPS is a rare malignancy with various colors, which can show aggressive nature. UPS should be differentiated from other conjunctival malignancies based on histopathological and immunohistochemical examinations including Ki-67.*

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Undifferentiated pleomorphic sarcoma (UPS), previously called as malignant fibrous histiocytoma (MFH), is a mesenchymal neoplasm that shows unidentifiable cellular differentiation when analyzed by presently available technology. MFH was first described in 1964, and was considered to be of probable fibrohistiocytic or fibroblastic lineage. Despite extensive immunohistochemical and ultrastructural studies, a true histiocytic origin was never shown. Moreover, several studies have shown that a significant subset of tumors diagnosed as MFH show a specific line of differentiation (lipogenic, neurogenic, myogenic, or nonsarcomatous), which has led to a general consensus that MFH represents a wastebasket of many tumors that share morphologic similarities. For this reason, MFH is now considered the obsolete terminology and has been replaced by the term UPS. UPS typically arises in the extremities, and soft tissues including the retroperitoneum, and rarely occurs in the periocular regions. Indeed, UPS arising in the conjunctiva is extremely rare. Here, we describe a case of 66-year-old male with UPS of the conjunctiva, and review the literature. This study adhered to the Declaration of Helsinki. Approval was not required from the Institutional review board of Hokkaido University as this is a single case report and literature review.

Methodology of the review of articles. Articles were searched *via* an academic search engine, PubMed, with items including 'fibrous histiocytoma' and 'conjunctiva', or 'undifferentiated pleomorphic sarcoma' and 'conjunctiva', with no limitation in the time period. This study excluded two reports describing locally aggressive fibrous histiocytomas. This study also excluded palpebral malignant fibrous histiocytoma (1). When the original reports were not available, we obtained information from secondary sources.

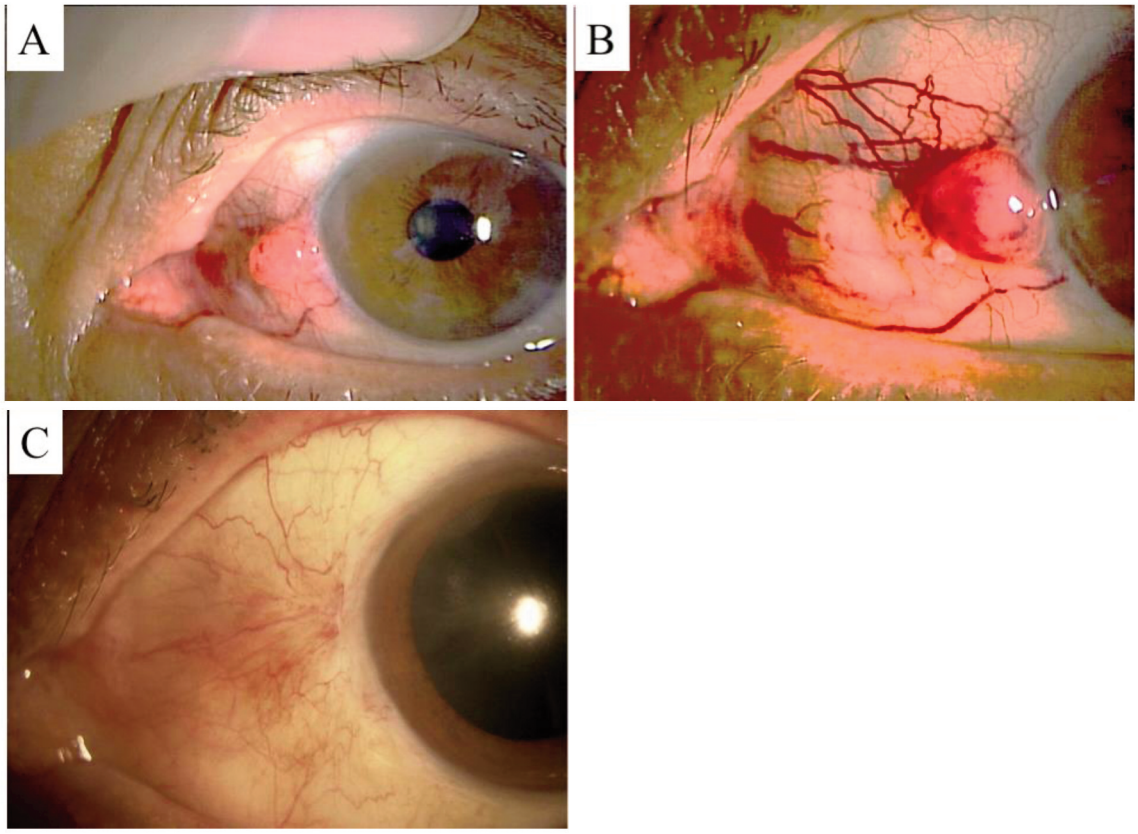

Figure 1. *Gross appearance of the conjunctival undifferentiated pleomorphic sarcoma. (A) A congested mass was observed on the medial conjunctiva of limbus of the left eye. (B) The mass enlarged after the mass was aspirated. (C) When the patient was referred to our hospital, conjunctival hyperemia was observed without tumor recurrence.*

Case Report

A 66-year-old man complained of a mass on the medial ocular surface, and visited a nearby hospital. He presented with a congested pink mass in the medial bulbar conjunctiva of his left eye (Figure 1A), which was suspected as a conjunctival cyst, and aspirated. After the aspiration, a slight bloody fluid was discharged, and the mass temporarily shrunk at the moment. However, since the mass enlarged and showed internal hemorrhage thereafter (Figure 1B), the mass was totally excised. The histopathological diagnosis was suspected of sarcoma. The patient was referred to our hospital to consult for the treatment strategy. He had neither medical history nor family history. His visual acuity was 20/20 in both eyes. Intraocular pressure was within the normal limit. Slit-lamp examination showed conjunctival hyperemia without tumor recurrence (Figure 1C). His cornea, anterior chamber, iris, and fundus were not remarkable. Whole-body computed tomography revealed no evidence of metastatic disease. We collected the specimens from the previous hospital and reassessed the histological findings. Histopathologically, the mass was a dome-shaped tumor covered by the conjunctival epithelium without atypia (Figure 2A). The surgical margin was free of tumor cells. The tumor comprised atypical short spindle cells growing as pattern-less pattern, with enlarged nuclei and eosinophilic cytoplasm (Figure 2B and C). Anisonucleosis, nucleus with irregular contour, prominent nucleoli, and mitotic figures (2.5 figures/high power fields) were also observed (Figure 2C). Some cells contained tiny vacuoles in the cytoplasm. No pigmentations were found in the tumor tissue. On immunohistochemistry, the tumor cells were positive for vimentin (Figure 2D), WT-1 (cytoplasm), p53 (a small number of cells showed weak-positivity), and Ki-67 (labeling index was 70%~80%) (Figure 2E), whereas they were negative for AE1/AE3, CAM5.2, p16, desmin, α-SMA, h-caldesmon, calponin, myogenin, MyoD1, S-100 protein, CD31, CD34, D2-40, HMB-45, SOX10, factor 8, KIT, p63, and CD68. The direction of cellular differentiation was undetermined; therefore, it was classified as UPS. After informed consent was obtained, we

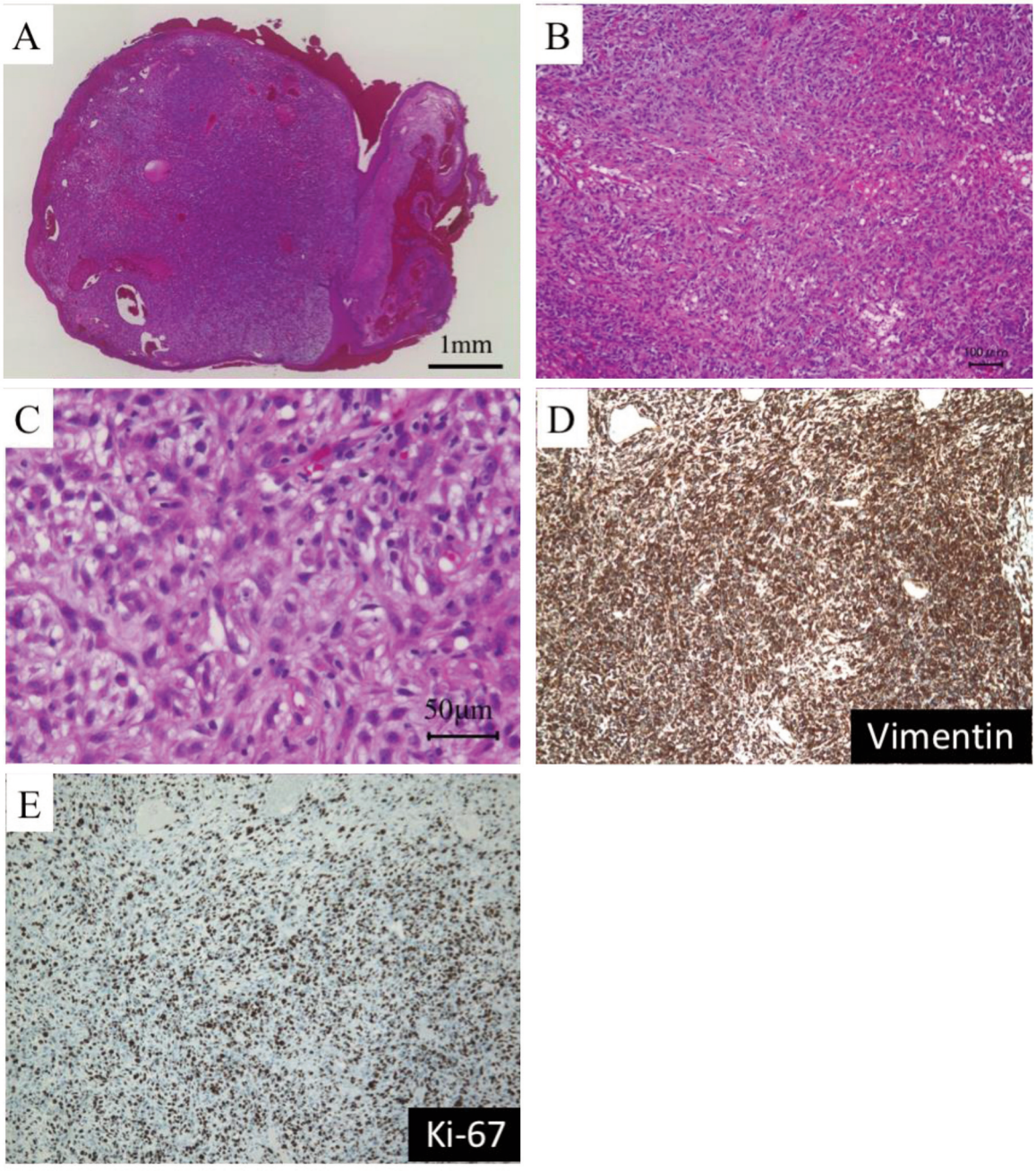

Figure 2. *Histopathological findings of the conjunctival undifferentiated pleomorphic sarcoma. (A) Histopathologically, the mass was elevated as a dome-shaped tumor covered by the conjunctival epithelium without atypia. The margin was negative (hematoxylin-eosin, ×40). (B) The tumor comprised atypical short spindle cells growing as pattern-less pattern, with enlarged nuclei and eosinophilic cytoplasm (hematoxylin-eosin, ×100). (C) Enlarged nuclei, anisonucleosis, nucleus with irregular contour, evident nucleoli and mitotic figures (2.5 figures/high power fields) were observed. Some cells contained vacuoles in the cytoplasm (hematoxylin-eosin, ×400). (D) The tumor cells were positive for vimentin. (×100). (E) The Ki-67 labeling index was 70%~80%. (×100).*

have observed the patient without additional treatment because the surgical margin was negative. No recurrence or metastasis was observed during the 2-year and 1-month follow-up.

Discussion

Tumors consisting of atypical spindle cells that can arise in the conjunctiva have been described as follows: spindle-cell

Table I. *Clinical features of this case and 12 cases with undifferentiated pleomorphic sarcoma previously reported in the literature.*

Case	Study (year) (ref. number)	Age (y)	Gender	Duration of lesion (mo)	Conjunctival location	Quadrant location	Basal diameter (mm)	Thickness (mm)	Tumor color	Initial diagnosis, initial treatment	Total excision (n)	Additional treatment	Recurrence (n)	Follow-up (mo)	Past medical histories
1	Delgado-Partida (1972) (9)	50	F	36	Limbus	Nasal	7	3	Yellowish	Pterygium s/o, excision	3	Enucleation	2	19	Not described
2	Urdiales-Viedma (1983) (10)	72	F	10	Limbus	NA	19	9	NA	Excision (details are unknown)	1	None	0	18	NA
3	Margo (1989) (11)	59	M	18	Bulbar	NA	12	NA	NA	Excision (details are unknown)	1	Exenteration parotidectomy	1	12*	NA
4	Pe'er (1990) (12)	3,5	F	NA	Bulbar	NA	12	7	Brown	Excision	1	None	NA	Lost	Xeroderma pigmentosum
5	Pe'er (1990) (12)	58	M	Several months	Limbus	Superonasal	15	4	Greyish	Pterygium, excision	2	Exenteration	1	50	Not described
6	Balestrazzi (1991) (13)	53	M	NA	Limbus	Temporal	NA	NA	NA	NA	4	Exenteration	3	18	NA
7	Allair (1999) (14)	60	M	9	Limbus	Nasal	4	NA	The color of the first lesion was not written, but the recurrence lesion involving the caruncle was pink.	Excision	4	Cryotherapy in second and third resection	3	12	Not described
8	Kim (2006) (15)	72	M	12	Limbus	Nasal	11	2	Tan	Excision	2	Cryotherapy, alcohol epithelio-lectomy of cornea, radiotherapy	0	80	Not described
9	Kim (2006) (15)	35	M	3	Limbus	Nasal	5	2	Tan	Excision	2	None	1	2	Not described

Table I. *Continued*

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Case	Study (year) (ref. number)	Age (y)	Gender	Duration of lesion (mo)	Conjunctival location	Quadrant location	Basal diameter (mm)	Thickness (mm)	Tumor color	Initial diagnosis, initial treatment	Total excision (n)	Additional treatment	Recurrence (n)	Follow-up (mo)	Past medical histories
10	Arora (2006) (16)	51	M	3	Bulbar	Temporal	7	NA	Fleshy, vascular	Completely excised in the sub conjunctival plane, with 3-mm conjunctival frill around the mass using a 'no-touch' technique.	2	Localized alcohol corneal epitheliole-ctomy, triple freeze-thaw cryopexy to the scleral base and edges of the conjunctiva	1	48	No history of trauma or prior ocular surgery
11	Milman (2007) (17)	51	F	Several months	Limbus	Supero-temporal	3	2	Hypervascular pink-gray	Penetrating keratoplasty	2 (biopsy for several times, penetrating keratoplasty 1, exenteration 1)	Cryotherapy, topical interferon α, mitomycin C, external beam radiation therapy (60Gy), exenteration	1	48	Systemic lupus erythema-tosus (SLE), SLE-related kerato-conjunctival epithe-liopathy
12	Boehlke (2007) (18)	25	F	4	Bulbar	Temporal	NA	NA	Pink	Pterygium s/o, biopsy	1 (biopsy 2, exenteration 1)	None	0	6	NA
	This case	66	M	3	Limbus	Nasal	5	4	Pink	Aspiration	1	None	0	25	None

Table II. *Histopathological features of this case and 12 cases with undifferentiated pleomorphic sarcoma previously reported in the literature.*

Case	Study (year) (ref. number)	Histological tumor depth of involvement	Mitotic activity per high power field	Ki-67	Vimentin	Smooth muscle actin	CD 68	S-100 protein	HMB45	CD34
1	Delgado-Partida (1972) (9)	Sclera and ciliary body	NA	NA	NA	NA	NA	NA	NA	NA
2	Urdiales-Viedma (1983) (10)	NA	NA	NA	NA	NA	NA	NA	NA	NA
3	Margo (1989) (11)	Sclera and ciliary body	NA	NA	NA	NA	NA	NA	NA	NA
4	Pe'er (1990) (12)	Cornea	Abnormal mitotic figures	NA	+	NA	NA	-	NA	NA
5	Pe'er (1990) (12)	Fornix and upper eyelid	Many	NA	+	NA	NA	-	NA	NA
6	Balestrazzi (1991) (13)	Orbital invasion	NA	NA	NA	NA	NA	NA	NA	NA
7	Allaire (1999) (14)	Deeper layers and corneal margins	Intense	NA	+(strong)	+	0,3	-	-	-
8	Kim (2006) (15)	Stroma	4-5	NA	+	+	+	-	-	-
9	Kim (2006) (15)	Stroma	<1	NA	NA	NA	+	-	NA	NA
10	Arora (2006) (16)	Tenon's layer	NA	NA	+	-	-	-	-	NA
11	Milman (2007) (17)	NA	Numerous	NA	+(diffuse)	+(focal)	+(focal)	-	-	-
12	Boehlke (2007) (18)	Lateral rectus muscle sheath	Frequent	+(in a few cells)	+(strong)	+(in some cells)	+ (strong)	NA	NA	+(strong)
	This case	Stroma	2,5	+(70~80%)	+	-	-	-	-	-

NA: Not available; +: positive.

carcinoma, melanoma, synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, Kaposi's sarcoma, and malignant peripheral nerve sheath tumor (MPNST). In this case, spindle-cell carcinoma and synovial sarcoma were excluded, because our case was negative for epithelial markers, AE1/AE3 and CAM5.2. Amelanotic melanoma was excluded, as S-100, HMB-45, and SOX-10 were all negative. Rhabdomyosarcoma was excluded, since the rhabdoid cells were not present, and desmin was immunohistochemically negative. Liposarcoma was excluded, since lipoblasts were not observed. Kaposi's sarcoma was excluded, as extravasated erythrocytes and hemosiderin were not observed in the tumor cells without CD34 immunoreactivity. Solitary fibrous tumor was excluded, as the tumor did not show typical staghorn-shaped blood vessel nor hemangiopericytoma-like vasculature, and CD34 was immunohistochemically negative. MPNST is an important differential diagnosis. MPNST is a malignant tumor with evidence of Schwann cell or perineurial cell differentiation (2). The positive rate of S-100 among cases of MPNST is 40–70% (2). Therefore, MPNST could not be excluded only by negativity for S-100. Loss of H3K27me3 expression was recently shown to be a highly specific marker for MPNST (2); however, H3K27me3 immunostaining was not performed, as the antibody was not available at the diagnosis of this case. Except for this, the immunostaining results did not show clear identifiable cellular differentiation, and were compatible with UPS, according to the WHO classification of tumors (3).

UPS is a mesenchymal neoplasm that shows unidentifiable cellular differentiation and is diagnosed following exclusion of other diseases (3). UPS was previously referred to as malignant fibrous histiocytoma, before WHO renamed it in 2002. With the re-classification, this term became a diagnosis of exclusion. Based on this new classification, UPS accounts for no more than 5% of adult soft tissue sarcomas (4). Histopathologically, the tumor is diffusely made up of spindle-shaped and epithelioid or polygonal cells with marked pleomorphism arranged in a haphazard, storiform, and fascicular growth pattern without obvious cellular differentiation (3).

In the ophthalmology field, it rarely occurs in the orbit (5), eyelid skin (6), palpebral conjunctiva (1), and bulbar and limbal conjunctiva. Among them, UPS of the conjunctiva is extremely rare. Among 1,643 conjunctival tumors, 4 cases (<1%) of fibrous histiocytoma have been reported; however, whether they were benign or malignant was not described (7).

So far, 13 cases of bulbar and limbal conjunctival UPS have been reported, (8-18) among which descriptions of 12 cases are available (Table I). The mean age of these 12 patients was 49 years (±19 years), which is younger than the age of cutaneous and subcutaneous UPS (72 years) (19). A reason for the younger onset of conjunctival UPS might be that self-detection is more likely as it presents as a mass on the ocular surface compared to that arising in other sites. There was no sex predilection among conjunctival UPS (the male to female ratio was 7 to 5), whereas 81.2% were male among cutaneous and subcutaneous UPS (19). Among 12 cases, 8 cases occurred in the limbus, whereas other 4 cases occurred in the bulbar conjunctiva. The color of the tumors differed depending on the case: yellow, tan, pink, brown, or vascularized. Among three cases, the initial diagnoses were pterygium. Initial therapies included biopsy or excision. Seven cases showed recurrence, and finally 1 and other 3 cases underwent enucleation and exenteration, respectively. The treatment for UPS is resection with tumor-free margins. In this case, the tumor was resected with negative margins; therefore, the eye has been observed without any additional treatment.

Although some cases of UPS described in other reports showed rapid growth, invasion into deeper tissues or recurrence (Table I), surprisingly labeling index for Ki-67, a common proliferative marker, was not fully described (Table II). Only Boehlke *et al*. have reported that a few tumor cell nuclei were positive for Ki-67 in the tissue of UPS (18). In contrast, Soon *et al*. reported that Ki-67 was negative in benign fibrous histiocytoma (20). Since this case showed a high Ki-67 labeling index measuring 70~80%, it was considered to have high proliferation activity. Therefore, Ki-67 index could contribute to the evaluation of proliferation activity in conjunctival UPS cases as well as to the differential diagnosis from benign fibrous histiocytoma.

In conclusion, conjunctival UPS is a rare malignancy with various colors, which can show potentially aggressive nature. UPS should be differentiated from other conjunctival malignancies based on histopathological and immunohistochemical examinations including Ki-67.

Conflicts of Interest

The Authors declare no conflicts of interest and no funding support regarding this study.

Authors' Contributions

Conception and design of the study: Satoru Kase. Acquisition and analysis of data: Yuka Suimon, Drafting the manuscript and figures: Yuka Suimon and Kase Satoru. Review and editing the manuscript: Tomoko Mitsuhashi and Susumu Ishida.

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