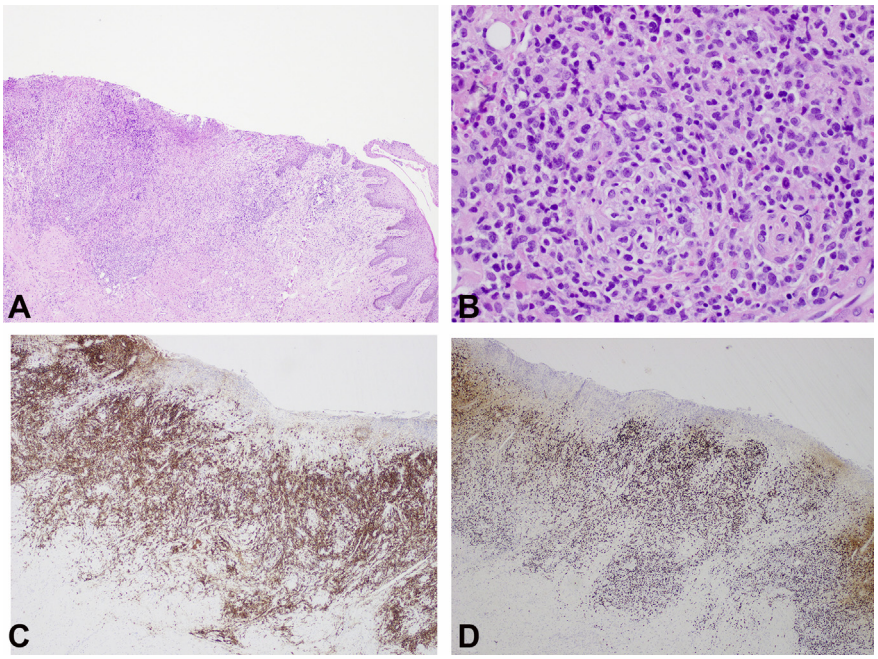

Fig. 1 Microscopy. (A) Low power of the lesion showing squamous mucosa with extensive ulceration. (B) High power image showing moderate infiltrate of atypical lymphoid cells. (C) The atypical lymphoid cells are strongly CD20 positive. (D) The atypical cells are strongly EBER positive.

medical history should always be taken to determine if the patient is on immunosuppressive medications. The current understanding of EBV-MCU is classically a self-limited condition. While no guidelines exist, management is conservative and includes withdrawal or decrease of immunosuppressant dose. Hence, pathologists must have knowledge of these diseases and a thorough clinicopathological investigation of this rare entity is important to avoid erroneous diagnosis and overtreatment.

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Mammary-type myofibroblastoma in the head and neck region

Sir,

Mammary-type myofibroblastoma (MTMF) is a mesenchymal tumour composed of cells with myofibroblastic differentiation initially described in the breast. It has been classified as benign by the World Health Organization (WHO) as it neither recurs locally nor metastasises.[1] Cytogenetic analysis of MTMF has identified consistent deletions at 13q resulting in the loss of tumour suppressor gene *Retinoblastoma* (*RB1*) at 13q14 chromosomal region, a genetic

alteration shared with spindle cell lipoma and cellular angiofibroma,[2] suggesting that these tumours should be grouped in the same family. While initially described in the breast, it is now increasingly recognised that MTMF can occur in a wide variety of anatomical locations including inguinal, intra-abdominal, truncal regions and lower extremities.[3] However, it is very rare in the head and neck region with limited numbers of case reports of MTMF involving the tongue and the infra-auricular region.[4,5] MTMF in the head and neck poses a significant diagnostic challenge, particularly on biopsy material as it closely mimics a spectrum of both benign and malignant spindle cell neoplasms. Accurate recognition of this benign entity is crucial in the head and neck to prevent radical surgical intervention.

We present a case of MTMF in the buccal cavity that highlights the diagnostic challenges and the significant role of clinical, radiological and morphological correlation, immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) studies.

A 58-year-old female was referred to the head and neck clinic in September 2017, for a swelling in left buccal mucosa which had been present for 6 months. She had no associated symptoms and denied any history of recent trauma or radiation exposure. The overlying skin was normal with intact sensation in upper and lower lips and no lymphadenopathy. Examination of the oral cavity revealed a 2 cm submucosal lesion under the left buccal mucosa, posterior to the oral commissure. An excisional biopsy with histopathological examination was performed at another institution and was favoured to represent dermatofibrosarcoma protuberans (DFSP). The patient was referred to a head and neck surgeon at our institution for the management of DFSP and the histopathology material from the external institution was submitted for review.

Histopathological examination showed a fragmented biopsy including deep soft tissues and skeletal muscle without overlying mucosa or skin. The neoplasm was composed of short intersecting fascicles of spindle shaped cells. The spindle cell fascicles entrapped skeletal muscle fibres without destruction of the muscle fibres (Fig. 1A). There were areas of collagenisation and focal storiform pattern. The spindle shaped cells showed indistinct cell membranes and short stubby nuclei with inconspicuous nucleoli (Fig. 1B). Entrapped adipose tissue was not present in the biopsies. Cellular pleomorphism, anisonucleosis, necrosis or mitosis were not seen. The material submitted for review also included immunostains for CD34, S100, p63, CD31 and SMA. Of these, the tumour cells showed strong diffuse immunostaining with CD34 (Fig. 1C) and had led to the lesion being designated as a DFSP.

A few additional differential diagnoses including solitary fibrous tumour (SFT) were considered at our institution on review in light of the submucosal location of the lesion at primary presentation rather than a subcutaneous location, nuclear features, presence of collagen and the relatively focal storiform pattern. Thus, a wider immunohistochemical panel including STAT6, desmin, β-catenin, MUC4, myogenin, cytokeratin AE1/AE3 and SOX10, were performed at our institution. The tumour cells demonstrated strong diffuse immunostaining with CD34 and desmin (Fig. 1D). The morphological and immunohistochemical pattern raised the differential diagnosis of MTMF. This was supported by patchy, moderate intensity immunostaining with oestrogen receptor. In the interim, the patient underwent a clinical examination by the head and neck surgeon at our institution and additional clinical and radiological details became available. The clinical examination demonstrated that the lump was discreet and freely mobile under the skin without any tethering, and contrast enhanced magnetic resonance imaging (MRI) indicated that the lump was relatively well circumscribed (Fig. 1E). The clinical and radiological findings coupled with the morphological features and immunohistochemical profile were in keeping with an MTMF. FISH was performed to strengthen the diagnostic confidence given the vast management and prognostic differences between DFSP and MTMF. Interphase FISH was performed for *RB1* using the ZytoLight SPEC RB1/13q12 dual colour probe (ZytoVision, Germany) and showed *RB1* deletion in the spindle cells (Fig. 1F). On the other hand, FISH for *PDGFB*, *COL1A1* and *USP6* ZytoLight SPEC dual colour break apart probes (ZytoVision) did not show rearrangements of these genes. Thus, the diagnosis was revised to MTMF, a benign spindle cell neoplasm. The lesion was excised with narrow margins in light of the rare diagnosis. Macroscopically it appeared as a well circumscribed yellowish lesion with a rubbery consistency (Fig. 1G) and the excision specimen showed typical morphological features of MTMF. The patient is currently well with no signs of disease.

MTMF is a benign mesenchymal tumour which is well entrenched in the soft tissue tumour literature with a large case series by Howitt *et al.* consisting of 143 cases.[3] MTMF occurs in both men and women, predominantly in the fifth and sixth decades but can occur at any age.[3] MTMF typically presents as a slow growing painless nodule. There are limited data in the literature regarding the radiological characteristics of MTMF. The published data suggest MTMF appears as a well-circumscribed mass on computed tomography (CT). MRI can show areas of fat signal within the tumour (bright on T1-weighted images but reduces with fat suppression) and the majority of tumours are bright on T2-weighted images.[6] Macroscopically MTMF tend to be well circumscribed with a rubbery to gelatinous cut surface. Histologically they are usually composed of short fascicles of spindle cells with short stubby nuclei and ill-defined cytoplasmic border. A hyalinised collagenous stroma is common and a variable amount of adipose tissue can be present. Cytological atypia is uncommon, however focal symplastic changes can be present. Mitotic activity is usually inconspicuous but can be up to 6 mitoses per 10 high power fields.[1] Necrosis is absent. Infiltrative growth is seen in some cases, mostly in intramuscular tumours.[3] MTMF is typically diffusely immunoreactive for desmin and CD34, CD99 and BCL-2.[3,7] There is variable immunoreactivity for smooth muscle actin (37%).[3] Oestrogen and progesterone receptors have been reported to be focally to diffusely expressed in 85% of cases.[7] Focal expression of h-caldesmon has been described in up to 50% of MTMF.[8] The characteristic recurrent genetic alteration of MTMF is deletions of 13q leading to loss of *RB1*.[1] Immunohistochemistry for Rb protein is also available.[9] Detection of *RB1* deletion using FISH or IHC is useful in confirming the diagnosis of MTMF.

The largest series by Howitt *et al.* includes only three examples from the head and neck.[3] In the head and neck, MTMF mimic a large number of spindle cell neoplasms with markedly different biological outcomes. Differential diagnoses include benign self-limiting entities such as nodular

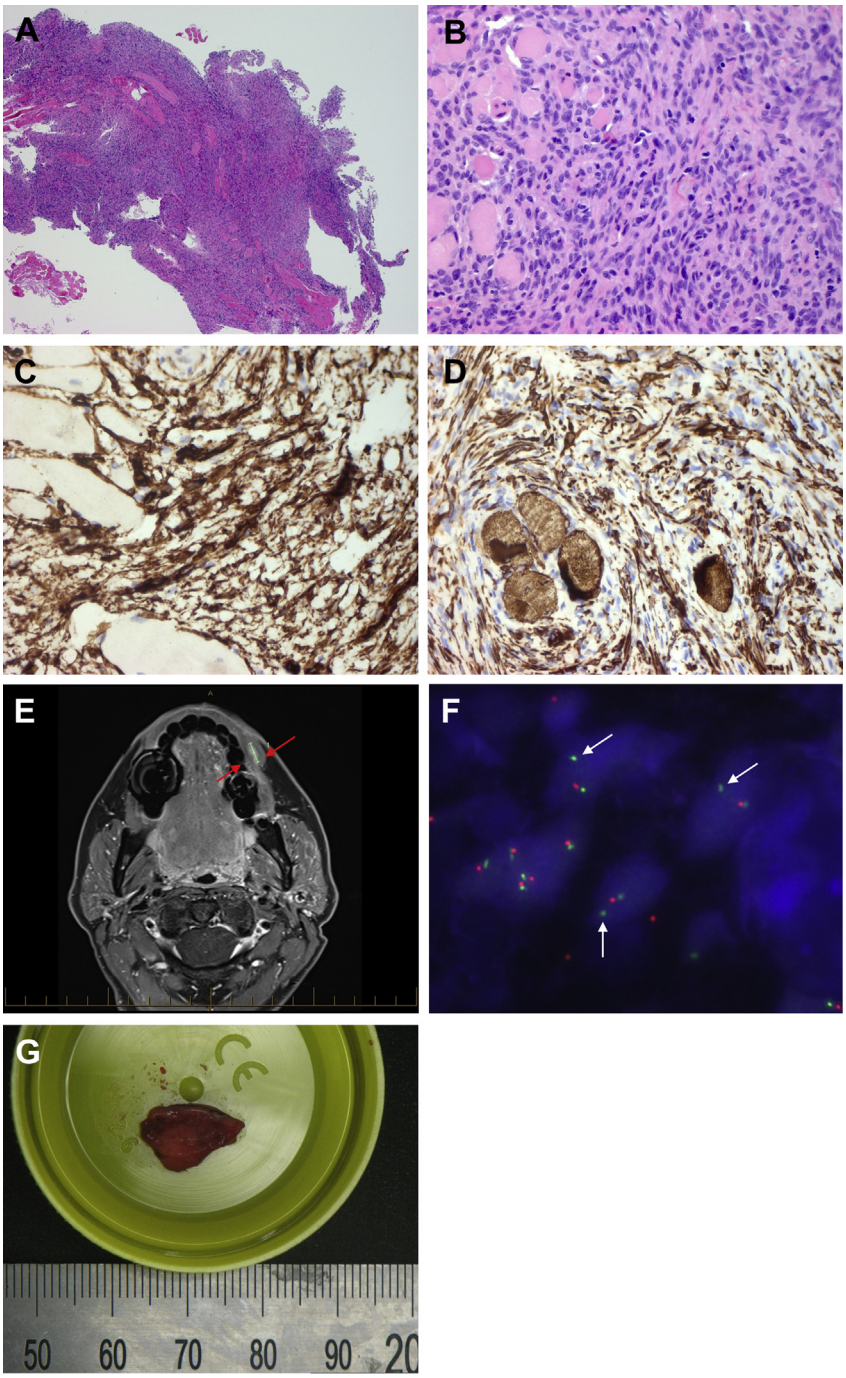

Fig. 1 (A) Low power and (B) high power of spindle cell lesion entrapping skeletal muscle fibres. (C) CD34 reactivity. (D) Desmin reactivity. (E) MRI showing well circumscribed mass in the left buccal space. (F) FISH showing deletion of *RB1* (loss of one red signal). (G) Macroscopic appearance of excision specimen with a well circumscribed, yellowish lesion.

fasciitis, leiomyoma and SFT; locally aggressive neoplasms requiring more extensive surgical approaches such as fibromatosis and DFSP and malignancies such as spindle cell carcinoma, melanoma, spindle cell rhabdomyosarcoma and malignant peripheral nerve sheath tumour (MPNST). Distinction of MTMF from other entities can be achieved using immunohistochemistry (Table 1).

Distinction of MTMF from DFSP and fibromatosis is of significant therapeutic and prognostic relevance. DFSP is more common in the head and neck as compared with MTMF. Interestingly, DFSP can also appear as a T2-hyperintense circumscribed mass,[10] thus making it difficult to radiologically distinguish from MTMF. DFSP is most likely to present as a subcutaneous lump, unless a recurrent lesion. It is also unlikely to be mobile. However, clinical information regarding the precise subcutaneous location of the nodule or its mobility may not always be readily and reliably available. Morphologically, MTMF can entrap skeletal muscle and tangential sectioning of its fascicular pattern can impart a storiform appearance as seen in this case, thus mimicking DFSP. While CD34 expression is the hallmark of DFSP, immunostaining for desmin and oestrogen has not been described in DFSP. Furthermore, both MTMF and DFSP show specific genetic alterations that can be assessed

Table 1 Immunophenotype in the differential diagnoses of MTMF

	MTMF	Nodular fasciitis	Leiomyoma	Fibromatosis	SFT	DFSP	Spindle cell carcinoma	MPNST	Spindle cell rhabdomyosarcoma
Cytokeratin	−	−	−	−	−	−	+	−	−
CD34	+	−	−	−	+	+	−	−/+	−
Desmin	+	−	+	−	−	−	−	−	+
SMA	−/focal +	+	+	−	−	−	−	−	−
ER	+/−	−	−	−	−	−	−	−	−
h-caldesmon	−/focal +	−	+	−	−	−	−	−	−
β-catenin	−	−	−	+	−	−	−	−	−
STAT6	−	−	−	−	+	−	−	−	−
S100	−	−	−	−	−	−	−	Focal +	−
Myogenin	−	−	−	−	−	−	−	−	+
MyoD1	−	−	−	−	−	−	−	−	+
FISH	*RB1* deletion	*USP6* rearrangement	−	−	−	*PDGFB* and *COL1A1* rearrangement	−	−	−

DFSP, dermatofibrosarcoma protuberans; FISH, fluorescence *in situ* hybridisation; MPNST, malignant peripheral nerve sheath tumour; MTMF, mammary-type myofibroblastoma; SFT, solitary fibrous tumour.

by FISH. It is essential to consider that in rare instances DFSP can show genetic changes other than *PDGFB-COL1A1* fusion.[11]

Accurate distinction from other aggressive malignancies is critical to avoid unnecessary radical surgeries with high morbidities. In this context, excluding a spindle cell carcinoma is important since these are much more common in the head and neck and may show aberrant loss of some cytokeratins. The presence of *in situ* carcinoma is diagnostically useful to identify spindle cell carcinoma, however may not be included in a small biopsy. Spindle cell carcinomas are more likely to show marked nuclear pleomorphism, anisonucleosis, nuclear membrane irregularities and mitoses in contrast to the monotonous stubby nuclei of MTMF. Spindle cell rhabdomyosarcoma can show bland cytological features, and can mimic benign neoplasms in a small biopsy.[12] Spindle cell rhabdomyosarcomas tend to show strap cells and demonstrate MyoD1 and focally myogenin (Myf5) expression in addition to desmin.

In conclusion, MTMF can rarely occur in the head and neck and requires a high index of suspicion and awareness of its morphological spectrum for accurate diagnosis of this benign entity. This case highlights the importance of clinical, radiological correlation with conventional histopathology, particularly while rendering diagnoses on small biopsy material. It also demonstrates the merit of employing a broad immunohistochemical panel that covers most cell lineages and differential diagnoses of spindle cell neoplasms.

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