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Review

Myoepithelial tumor of soft tissue and bone: A current perspective

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Summary. Myoepithelial tumor (MET) of soft tissue and bone is an unusual tumor of uncertain differentiation and histogenesis, but lately has been recognized as a distinct tumor entity. This tumor forms a morphologic continuum with a mixed tumor and a parachordoma, but is different from an extra-axial chordoma or chordoma peripheriсium. METs display a range of histopathologic features, including architectural arrangements/growth patterns, cell types and intervening stroma, leading to their several differential diagnoses. Presently, moderate nuclear atypia is the acceptable criterion to differentiate a myoepithelial carcinoma from a myoepithelioma. Immunohistochemical (IHC) stains, including epithelial antibody markers, along with S100 protein and GFAP are necessary in confirming a diagnosis of a MET. Certain METs are associated with loss of INI1/SMARCB1. Lately, certain specific "molecular signatures" been described underlying METs, identification of which that can further aid in their accurate diagnosis and in differentiating these tumors from their diagnostic mimics. Complete surgical resection forms the treatment mainstay, irrespective of a myoepithelioma or a myoepithelial carcinoma. This review will focus upon clinicopathologic, immunohistochemical and molecular features of METs of soft tissue and bone, along with their differential diagnoses and diagnostic implications.

Key words: Myoepithelial tumor of soft tissues, Intraosseous myoepithelial tumor, Myoepithelioma, Myoepithelial carcinoma, EWSR1, INI1

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Introduction

Primary myoepithelial tumor (MET) of soft tissues is rare, but a well-defined tumor, of uncertain histogenesis. One of the first cases of a MET of the soft tissues was published by Burke et al. (1995) in a retroperitoneal location, diagnosed with the help of immunohistochemical (IHC) stains and further confirmed by ultrastructural examination. This was followed by a series of 19 METs of soft tissues, documented by Kilpatrick and Fletcher (Kilpatrick et al., 1997). Subsequently, there have been case reports and studies regarding these tumors, documented by various investigators (Burke et al., 1995; Kilpatrick et al., 1997; Michal and Miettinen, 1999; Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Antonescu et al., 2010; Rekhi et al., 2012). These tumors occur over a wide age-range, but are mostly seen in middle-aged patients and affect both the sexes equally (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Antonescu et al., 2010). Primary MET has also been described in the bones as a distinct tumor entity (de Pinieux et al., 2001; Kurzawa et al., 2013; Rekhi et al., 2014, 2016).

METs of soft tissues and bones exhibit a wide histopathologic spectrum and are synonymous with mixed tumors, myoepitheliomas and parachordomas (Kilpatrick et al., 1997; Antonescu et al., 2010; Rekhi et al., 2012; Fletcher et al., 2013). As a result of significant heterogeneity within METs, several soft tissue and bone tumors constitute as their differential diagnoses. Application of IHC markers is necessary for making a correct diagnosis of a MET (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Kurzawa et al., 2013; Rekhi et al., 2012, 2016). The diagnosis of a malignant MET or a myoepithelial carcinoma is based upon the presence of at least moderate nuclear atypia (Hornick and Fletcher,

2003; Rekhi et al., 2012, 2016 Kurzawa et al., 2013). Lately, various molecular alterations have been unraveled that constitute as the molecular signatures of certain soft tissue METs, including myoepithelial carcinomas (Antonescu et al., 2010, 2013; Agaram et al., 2015).

This review will focus upon clinical, radiologic, histopathologic, IHC and molecular features of METs of soft tissue and bones, along with a mention of diagnostic implications, including treatment and outcomes in such cases.

Clinical features

METs of soft tissues and bone occur in patients of all age groups. These tumors have been reported in newborns, as well as in patients in the tenth decade of life. However, these tumors are most commonly seen in middle-aged patients, with a mean age of 38 years, as documented in the largest series (Michal and Miettinen, 1999; Hornick and Fletcher, 2003; Gleason and Fletcher, 2007).

In a series of 8 primary intraosseous METs, the reported average age was 33.5 years, while in a recently documented series of 5 intraosseous myoepithelial carcinomas, the reported average age was 26.2 years (Kurzawa et al., 2013; Rekhi et al., 2016). Gleason et al (Gleason and Fletcher, 2007) observed that METs in children are significantly more likely to be malignant and aggressive than those occurring in adults. They observed that nearly 62% METs in children and 42% in adults were malignant (Gleason and Fletcher, 2007). Gender-wise males and females have been found to be equally affected in most documented studies (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Antonescu et al., 2010).

The presenting clinical symptoms in patients afflicted with these tumors depend upon the sites of involvement. Patients most commonly present with a painless mass, followed by a painful mass (more common in superficial METs). Cutaneous METs are known to present as cutaneous papules. Rarely, patients present with only pain or neurological symptoms, such as paraesthesia. Deep-seated METs are identified incidentally. The duration of symptoms ranges from a few weeks to decades, with a mean of 4 years (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Kurzawa et al., 2013).

Site-wise, METs mostly occur in the acral region and in the girdles, commonly in the lower limbs. Other sites include trunk and head and neck region. Rarely, METs have been reported in the scrotal skin and in the visceral organs, such as lungs (Hornick and Fletcher, 2003; Flucke et al., 2011). These tumors are more commonly superficially located. In the deeper tissues, these might present either in the subfascial, intramuscular regions, or rarely, in the intraosseous sites. Approximately 9% METs are known to present as intraosseous masses (Hornick and Fletcher, 2003; Antonescu et al., 2010). Among intraosseous METs, a myoepithelioma is seen more frequently in the appendicular bones, while a myoepithelial carcinoma is more commonly documented in the axial bones (Kurzawa et al., 2013; Rekhi et al., 2016). The size of the tumor ranges from 0.3 to 21.6 cm. Cutaneous and superficial METs are smaller than those occurring in deeper locations (Hornick and Fletcher, 2003; Flucke et al., 2011; Rekhi et al., 2012). In the largest study on METs of soft tissues, Hornick et al (Hornick and Fletcher, 2003) observed an average tumor size of 4.7 cm. They also found that the malignant tumors (average=5.9 cm) were significantly larger than their benign counterparts (average 3.8 cm) ($p=0.01$) (Hornick and Fletcher, 2003).

Radiologic features

Radiologic features of METs of soft tissue have not been well described. However, radiologic features of primary intraosseous METs have been described in case reports, as well as in case series (de Pinieux et al., 2001; Rekhi et al., 2011, 2016; Kurzawa et al., 2013).

On radiologic examination, primary intraosseous METs appear as lytic lesions with sclerotic margins. At the same time, METs appearing as sclerotic lesions have also been reported (Rekhi et al., 2011; Kurzawa et al., 2013). On magnetic resonance imaging (MRI), METs occurring in the soft tissues appear as well-defined lobulated tumors (Fig. 1A,B). The tumor mass is centered within the bone, but a few reported cases appeared as expansile masses (Kurzawa et al., 2013; Rekhi et al., 2016). Some tumors are known to show periosteal new bone formation. Larger sized and malignant METs show bone destruction with cortical erosion, breach and soft tissue extension (Kurzawa et al., 2013; Rekhi et al., 2016). These tumors are of homogenous intensity on computed tomographic scans and show multiple lobules, internal septa and well-defined borders (de Pinieux et al., 2001). On Magnetic resonance imaging (MRI), T1-weighted images of the tumor show hypointense signals and T2-weighted images show hyperintense or heterogeneous signals. A uniform enhancement with gadolinium is noted. METs of soft tissues show similar findings on MRI scans (Rekhi et al., 2016).

Radiologically, the differential diagnoses of a soft tissue MET include a range of soft tissue tumors, whereas the differential diagnoses of an intraosseous MET, including a myoepithelial carcinoma are giant cell tumor of bone, aneurysmal bone cyst, an adamantinoma, an osteosarcoma and a chondrosarcoma (Rekhi et al., 2011, 2016).

Histopathologic features

On gross examination, these tumors are mostly unencapsulated, well-circumscribed and show a lobulated appearance. The malignant METs display infiltrative margins. These tumors are variable in

consistency and are soft to firm/ rubbery to hard, depending upon the intervening stroma that could be myxoid to chondroid to osteoid. The color varies from white to yellow to tan, the latter in case of hemorrhage. The cut surface is glistening, mucoid and myxoid. Trabeculations and microcysts are seen, along with occasional cases showing foci of calcification, necrosis and hemorrhage (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Rekhi et al., 2012; Kurzawa et al., 2013).

Microscopically, the tumors are unencapsulated, lobulated and circumscribed with focal infiltrative margins; the latter feature is more commonly identified in myoepithelial carcinomas. A range of cellular arrangements, cell types and stroma/ matrix is seen within METs. The tumor cells are arranged in nodules and are arranged in the form of cords, trabeculae, as well as in a nesting pattern; sheet-like and in a reticular pattern (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007). Rare cellular patterns include tubulo-acinar, pseudoacinar, alveolar and 'rhythmic palisades' (Rekhi et al., 2012). Most common cell-type is polygonal/epithelioid, containing moderate to abundant, eosinophilic cytoplasm, followed by cells with clear cytoplasm (mostly in parachordomas) and cells with spindle-shaped nuclei. Gradual transition from one cell type to another is often seen. Other cell types seen are plasmacytoid, rhabdoid and small round cell types (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Rekhi et al., 2012, 2016; Kurzawa et al., 2013). The round cells with scant cytoplasm are more commonly seen in pediatric cases (approximately 30% of the cases) (Gleason and Fletcher, 2007). Certain tumors show ducts and tubules with sharply defined

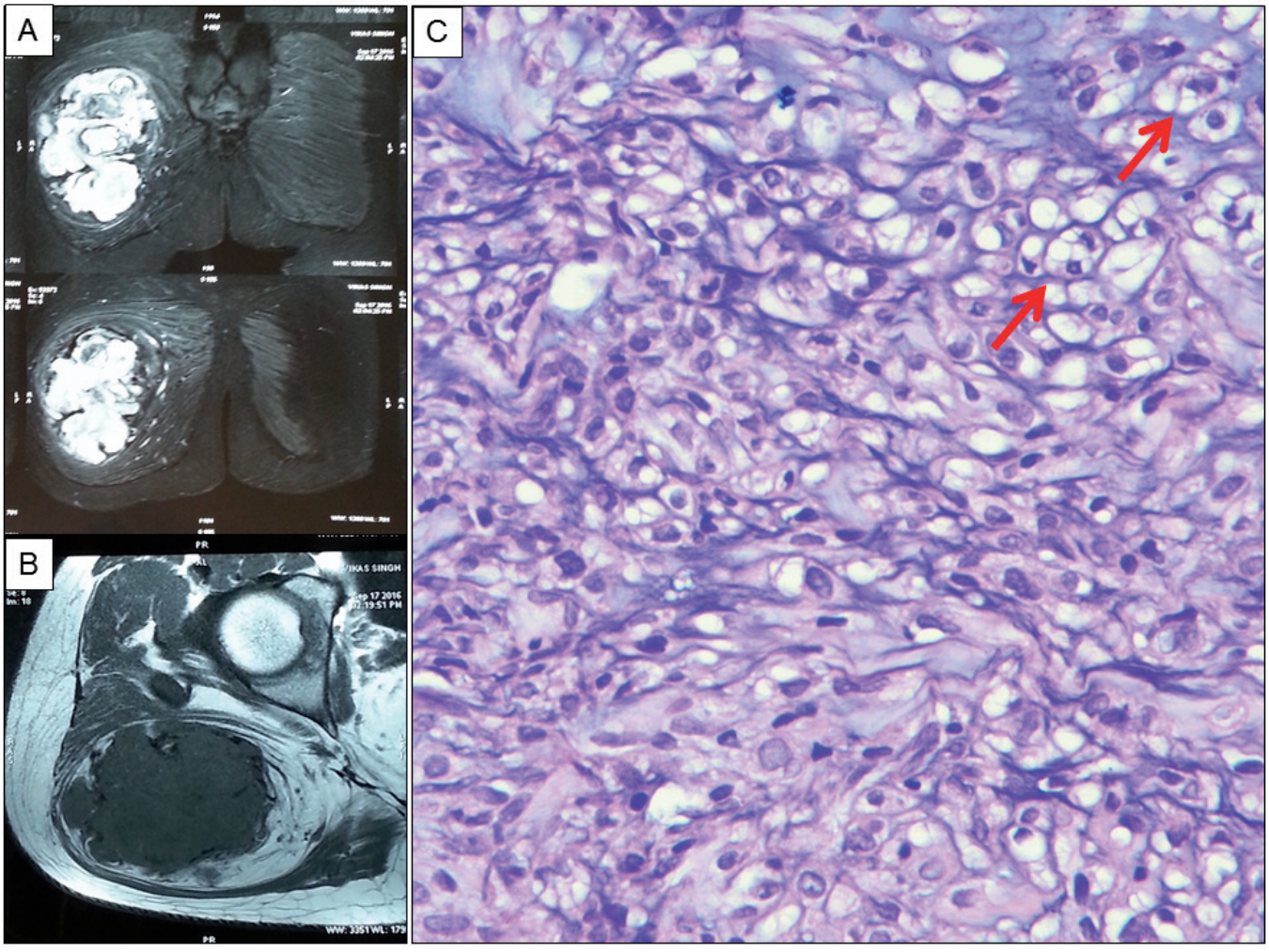

Fig. 1. Myoepithelioma of soft tissues. Magnetic resonance imaging (MRI) (post-contrast) showing a well-defined, lobulated soft tissue tumor in the gluteal region. **B.** T1-axial image showing a well-defined, multilobulated tumor, isointense to the muscles. **C.** Microscopic examination showing polygonal cells, including cells with vacuolated cytoplasm (arrows), embedded in a myxochondroid matrix. Hematoxylin-eosin (H and E) x 200.

luminal borders along with myoepithelial cells. These are classified as mixed tumors (Hornick and Fletcher, 2003). The intervening matrix in most tumors is myxoid or chondromyxoid type. Some tumors display a collagenous stroma or a combination of myxoid and collagenous stroma. At the same time, a significant proportion of METs might not show any stroma (Hornick and Fletcher, 2003). Metaplastic cartilage, bone formation, calcification and adipocytic differentiation are also frequently seen (Hornick and Fletcher, 2003; Flucke et al., 2011). Rarely, squamous metaplasia has been described in certain primary intraosseous myoepitheliomas, as well as in intraosseous myoepithelial carcinomas (Rekhi et al., 2011, 2016).

Parachordoma and an ectomesenchymal chondromyxoid tumor (ECT) of the tongue, initially thought to represent different tumor entities are now considered as a part of the common spectrum of METs (Hornick and Fletcher, 2003; Argyris et al., 2016). The term parachordoma was first coined by Dabska (Dabska, 1977), but this tumor was first described by Laskowski (Dabska, 1977; Fisher and Miettinen, 1997) in 1951, as chordoma periphericum. As a result of its morphologic similarity with a classical chordoma, various authors suggested that this tumor might be representative of an abaxial chordoma (Dabska, 1977; Shin et al., 1994). However, recent studies have shown that a parachordoma is different from an extra-axial or an abaxial chordoma/ chordoma periphericum (Tirabosco et al., 2008; Rekhi et al., 2012).

Microscopically, parachordomas are composed of polygonal cells with an abundant, pale to eosinophilic and vacuolated cytoplasm, embedded in a hyaline and myxoid matrix. A transition of these polygonal-shaped

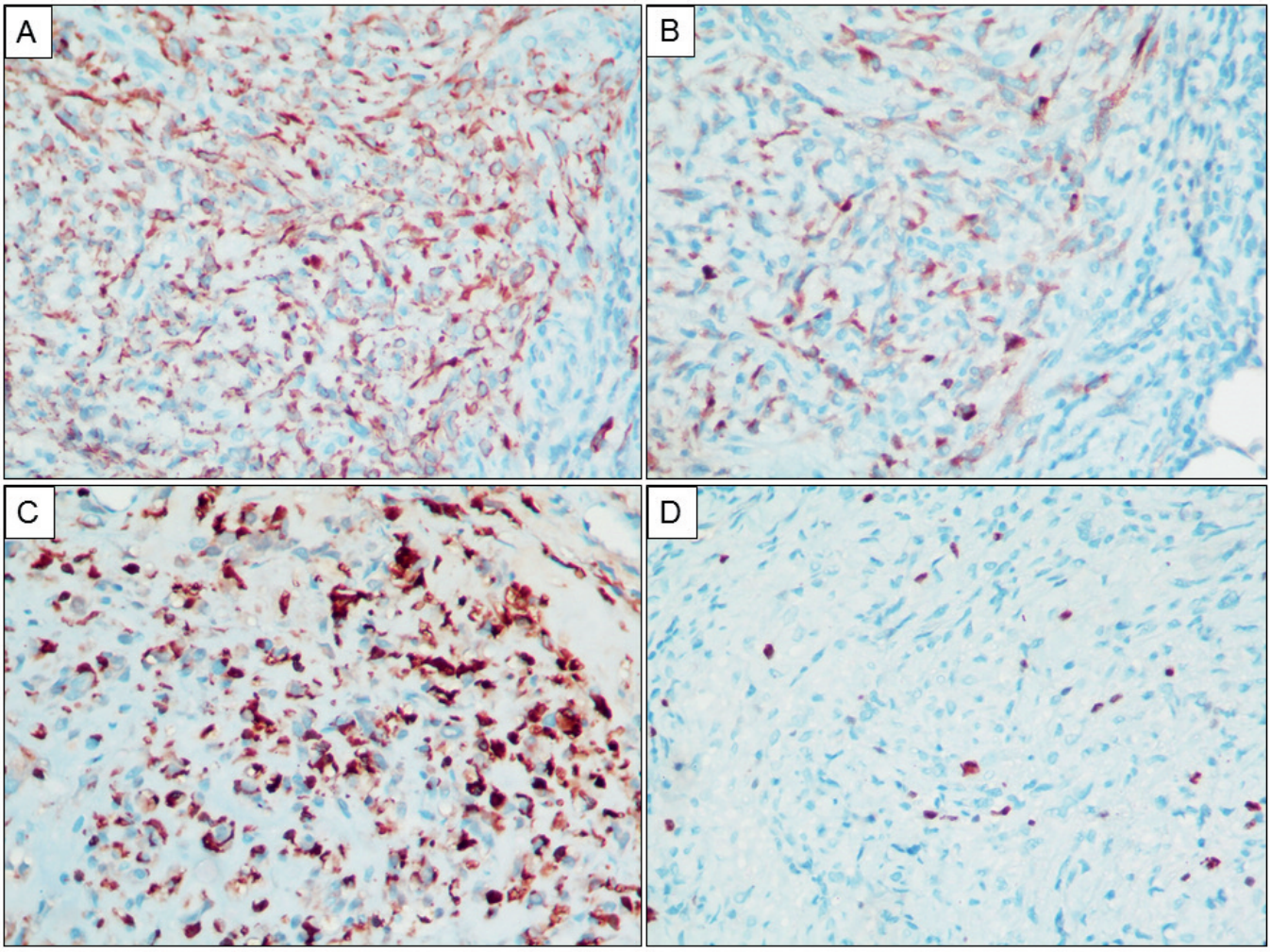

Fig. 2. Immunohistochemical results of the same case. **A.** Tumor cells displaying pan cytokeratin (AE1/AE3) positivity. **B.** Focal EMA positivity within tumor cells. **C.** S100 protein positivity in several tumor cells. **D.** Low Ki-67/MIB1 highlighting nearly 5% tumor cell nuclei. Diaminobencidine (DAB). x 400.

cells to spindle-shaped cells is noted in parachordomas and is also a rare feature of a chordoma (Fisher and Miettinen, 1997). In a retrospective study, Fisher et al (Fisher and Miettinen, 1997) concluded that a chordoma and a parachordoma are different entities, as chordomas have an aggressive clinical behavior, higher metastatic rate and mortality, in contrast to parachordomas. Kilpatrick et al (Kilpatrick et al., 1997) noted that an MET of soft tissues might focally show vacuolated cells, resembling parachordomas. Furthermore, in a larger study, Hornick et al (Hornick and Fletcher, 2003) confirmed that parachordomas are within the spectrum of METs. An ectomesenchymal tumor (ECT) shows polygonal to epithelioid cells in a chondromyxoid stroma (Argyris et al., 2016). This tumor was described as a pathological entity by Smith et al (Smith et al., 1995), who proposed that these tumors originate from ectomesenchymal cells in the tongue. However, after further IHC and molecular results, ECTs have been included within the morphologic continuum of a MET (Smith et al., 1995; Argyris et al., 2016).

As result of their biphenotypic nature, METs express a range of IHC markers, including epithelial and myoepithelial markers. In most of the documented series

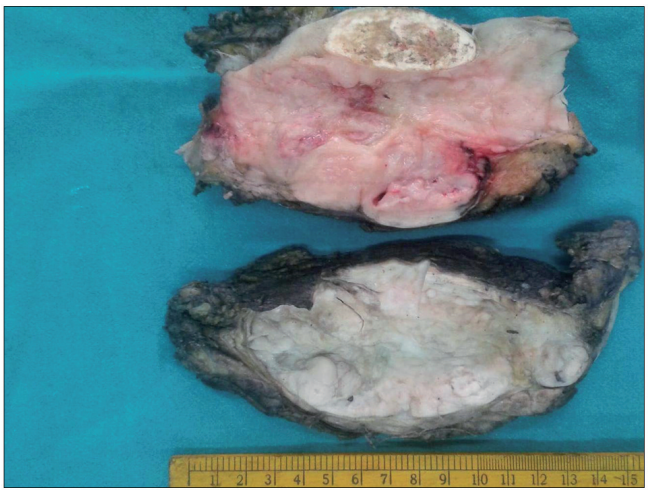

Fig. 3. Gross appearance of a myoepithelial tumor involving bone and soft tissues. Cut surface, fresh and fixed state showing a grey-white, lobulated, rubbery tumor with focal glistening areas.

Table 1. Review of molecular results from various studies on myoepithelial tumors of soft tissues and bone.

Authors, Year	Gene Rearrangement	Positive Cases	Fusion Partner
Brandal et al., 2008	EWSR1 (n=1)	1	ÈWSR1-PBX1
Brandal et al., 2009	EWSR1 (n=1)	1	EWSR1-ZNF444
Antonescu et al., 2010	EWSR1(n=66)	30	EWSR1-POU5F1(n=5)
			EWSR1-PBX1(n=5)
			EWSR1-ZNF444(n=1)
			EWSR1-#(n=19)
	FUS(n=30§)	1	FUS-#
Flucke et al., 2011 (Cutaneous Mixed tumors/Myoepithelioma)	EWSR1(n=16)	7	EWSR1-*
	FUS(n=9§)	0	-
Rekhi et al., 2012	EWSR1(n=6)	3	EWSR1-*
Bahrami et al., 2012	PLAG1(n=11)	8	PLAG1-*
Flucke et al., 2012	EWSR1(n=1)	1	EWSR1-ATF1
Romeo et al., 2012	EWSR1(n=7)	1	EWSR1-NFATC2
Antonescu et al., 2013	PLAG1(n=35‡)	12	PLAG1-LIFR(n=1)
			PLAG1-CTNNB1(n=0)
			PLAG1-#(n=11)
Kurzawa et al., 2013 (Intraosseous Myoepithelial tumors)	EWSR1(n=7)	5	EWSR1-PBX1(n=1)
			EWSR1-*(n=4)
Puls et al., 2014	FUS(n=1)	1	FUS-POU5F1
Agaram et al., 2015	EWSR1(n=23§§)	3	EWSR1-PBX3
Huang et al., 2015	FUS(n=66‡‡)	6	FUS-KLF17(n=4)
			FUS-#(n=2)
	EWSR1(n=16§§)	1	EWSR1-KLF17
Rekhi et al., 2016	EWSR1(n=1)	1	EWSR1-*
Argyris et al., 2016 (Ectomesenchymal chondromyxoid tumor)	EWSR1(n=11)	3	EWSR1-*
	PLAG1(n=7)	0	-

*: Fusion partner not tested, #: Fusion partner not identified, §: Tested in a cohort of cases lacking EWSR1 gene rearrangement, §§: Tested in a cohort of cases with EWSR1 gene rearrangement with an unknown fusion partner, ‡: Tested in a cohort of cases lacking EWSR1 and FUS gene rearrangement, ‡‡: Tested in a cohort of cases lacking EWSR1 and PLAG1 gene rearrangement.

of METs, pan cytokeratin (AE1/AE3), epithelial membrane antigen (EMA) or cytokeratin (CK) was found to be positive in more than 90% cases (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007). Hornick and Fletcher (2003) recommended an optimal IHC panel for diagnosis of a MET, including markers, such as EMA, AE1/AE3, S100 protein and glial fibrillary acidic protein (GFAP) (Hornick and Fletcher, 2003). They recommended positive expression of at least a single epithelial IHC marker (EMA and or AE1/AE3), along with the positive expression of myoepithelial markers (S100 protein and/or GFAP), as a minimum criteria for substantiating a diagnosis of a MET. Subsequently, Rekhi et al. (2012) in a series of 14 METs, including myoepithelial carcinomas of soft tissues, observed EMA positivity in 10/12 tumors (83%), CK positivity in 3/12 tumors (25%), along with S100 protein and glial fibrillary acidic protein (GFAP) in (11/13, 85%) and, (6/12, 50%) tumors, respectively. In equivocal cases, they recommended p63, CD10, calponin and SMA as additional, useful, surrogate markers (Rekhi et al., 2012).

In their study, Kurzawa et al. (2013) reported EMA positivity in 7/8 primary intraosseous METs and negativity for keratins (AE1/AE3 or CK or Cam5.2) in all their 8 cases. Recently, Rekhi et al (Rekhi et al., 2016) reported positive expression of various epithelial makers, such as EMA (5/5), CK (1/1) and CK5/6 (4/4), along with S100 protein (5/5) and GFAP (3/5), in 5 cases of primary intraosseous myoepithelial carcinomas.

EMA positivity has been reported within the range of 20% and 100% and approximately, including in 63% cases, in the largest documented series of METs, including carcinomas (Kilpatrick et al., 1997; Hornick

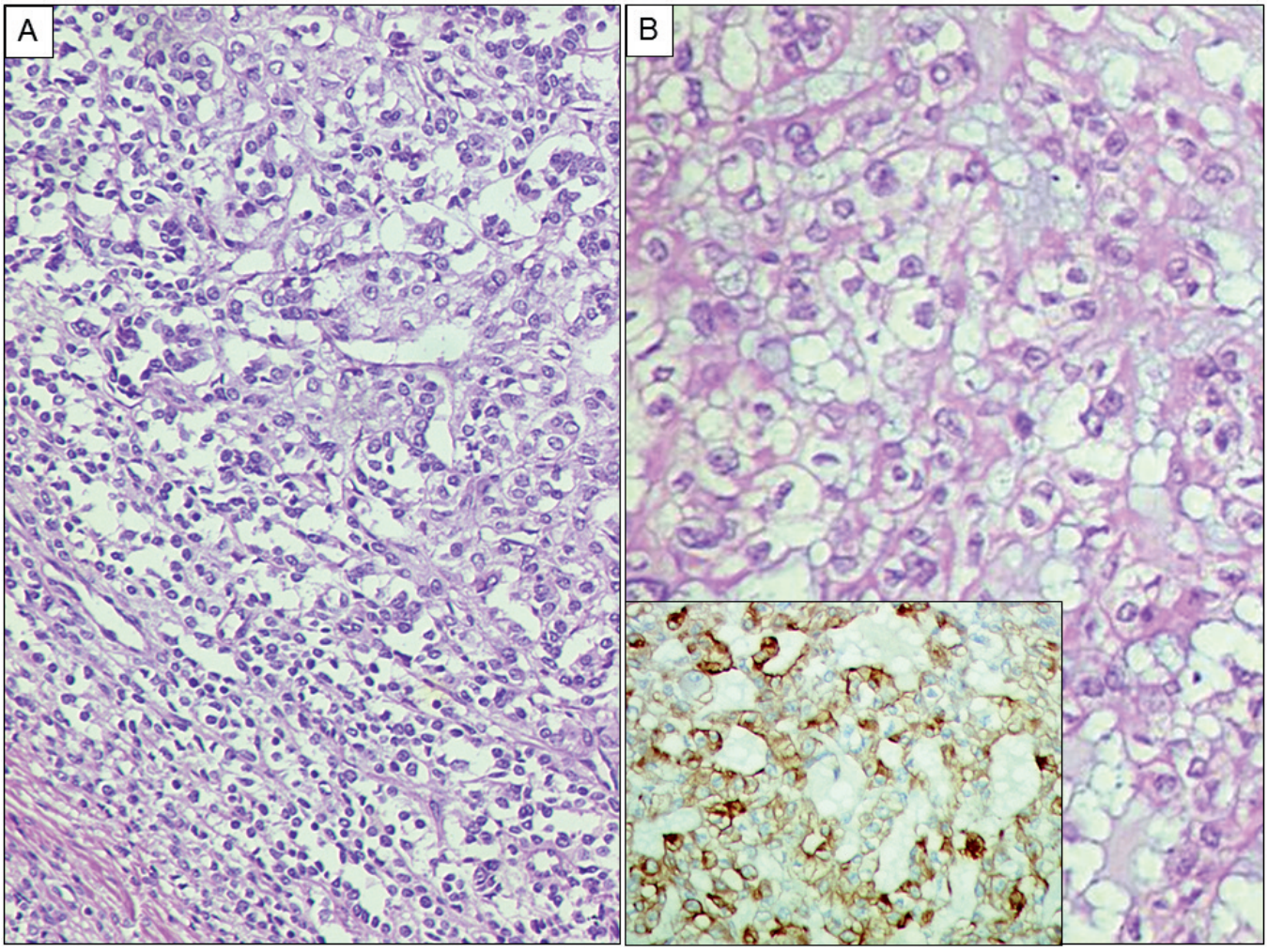

Fig. 4. Same case. Myoepithelioma. Microscopic findings. **A.** Cellular tumor composed of benign appearing round to polygonal cells arranged in cords and nests with intespersed thin walled blood vessels and myxoid stroma. H and E. **B.** Higher magnification displaying polygonal cells with clear cytoplasm, embedded in a myxoid matrix. H and E. Inset: tumor cells displaying pan cytokeratin (AE1/AE3) positivity. DAB. A, x 200; B, inset, x 400.

and Fletcher, 2003; Gleason and Fletcher, 2007; Kurzawa et al., 2013; Rekhi et al., 2016). S100 protein immunoexpression has been reported within the range of 72% and 100% within METs of soft tissues and bone (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Rekhi et al., 2012; Kurzawa et al., 2013). P63 positivity is seen between 23% and 70% tumors and GFAP expression within 27% and 60% METs (Kilpatrick et al., 1997; Hornick and Fletcher, 2003; Rekhi et al., 2012, 2016). The most commonly expressed myogenic marker in these tumors is calponin, which is reported in 86% to 100% of cases, followed by SMA which is documented in 36-64% of cases and desmin in 0-20% of cases (Kilpatrick et al., 1997; Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Rekhi et al., 2012; Kurzawa et al., 2013). CD10 positivity is seen in approximately 67% of METs (Rekhi et al., 2012). Focal cytoplasmic and membranous staining for MIC2 (CD99) is reported in approximately 80% of cases, particularly in the round cell component of METs (Gleason and Fletcher, 2007). SOX10 (Schwannian/melanocytic marker) expression is more commonly seen in benign METs (80%), as compared to the malignant counterparts (30%) (Miettinen et al., 2015).

Nearly 40% METs have been reported to display loss of integrase interactor 1 (INI1)/SMARCB1/BAF47 protein and are therefore included under the expanding spectrum of "INI1 deficient" tumors (Gleason and Fletcher, 2007; Rekhi et al., 2012). Nuclear reactivity for PLAG1 antibody, which is seen in pleomorphic adenoma, is only seen in mixed tumors and not in myoepitheliomas. The staining is more diffuse in the

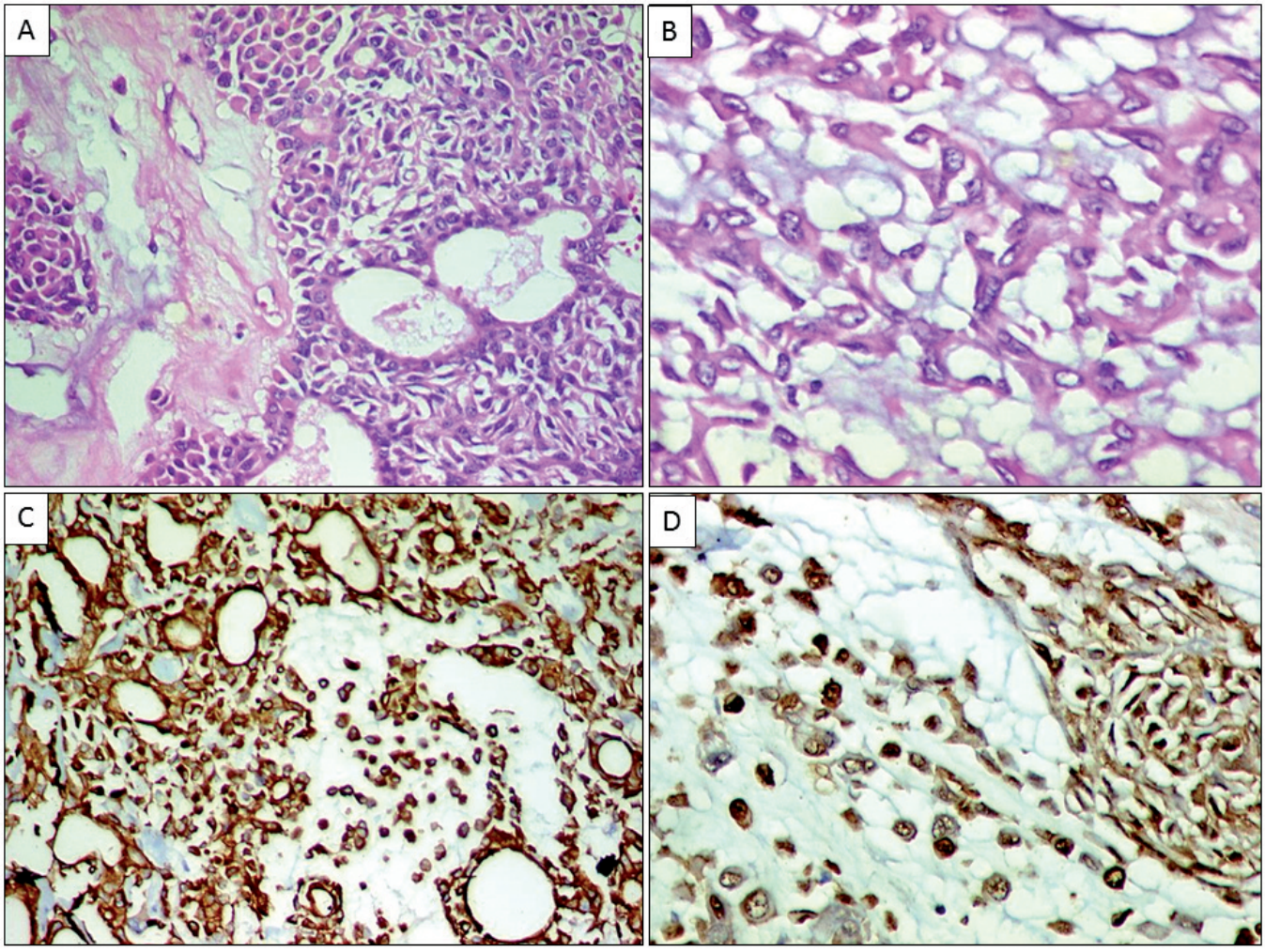

Fig. 5. A. Tumor composed of polygonal cells arranged in diffuse and tubular manner (mixed epithelial tumor) with interspersed cystic areas and collagenous stroma. Hematoxylin-eosin (H and E). **B.** Higher magnification showing rather benign apearing tumor cells with eosinophilic cytoplasm, arranged in cords and trabeculae within abundant myxoid stroma. H and E. **C.** Tumor cells showing diffuse pan cytokeratin (AE1/AE3) positivity. DAB. **D.** Tumor cells displaying S100 protein positivity. DAB. A, x 200; B-D, x 400.

myoepithelial component and is focal to absent in the epithelial cells. PLAG1 expression correlates well with *PLAG1* gene rearrangement (Jo and Fletcher, 2015). Brachyury is not expressed in a MET/parachordoma, in contrast to an abaxial/extra-axial chordoma or a chordoma peripheric um, supporting the view that these two categories of tumors are different (Rekhi et al., 2012, 2016).

Criteria for malignancy are not well-defined in METs of soft tissue and bone, unlike in the salivary gland tumors (Kilpatrick et al., 1997; Michal and Miettinen, 1999; Savera et al., 2000; Hornick and Fletcher, 2003; Gleason and Fletcher, 2007). In salivary gland METs, tumor infiltration beyond the capsule into the adjacent salivary gland constitutes the acceptable criterion for malignancy (Savera et al., 2000). There is no consensus regarding cytologic atypia and mitotic figures in salivary gland METs. In case of primary soft tissue and intraosseous METs, presence of at least moderate nuclear atypia is presently considered as the criteria for malignancy (Kilpatrick et al., 1997; Hornick and Fletcher, 2003; Rekhi et al., 2012, 2016; Fletcher et al., 2013; Kurzawa et al., 2013). In their premier study, Hornick and Fletcher (Hornick and Fletcher, 2003) classified tumors with benign cytomorphology or mild cytologic atypia (low-grade) as myoepithelioma or mixed tumor and tumors with moderate to severe atypia (high-grade) as myoepithelial carcinoma (epithelioid or spindle-shaped cells with vesicular or coarse chromatin, prominent, often large nucleoli, or nuclear pleomorphism) or malignant mixed tumor (malignant bone or cartilage). In another study, Gleason and Fletcher (Gleason and Fletcher, 2007) analyzed a series of myoepithelial carcinomas, occurring in children,

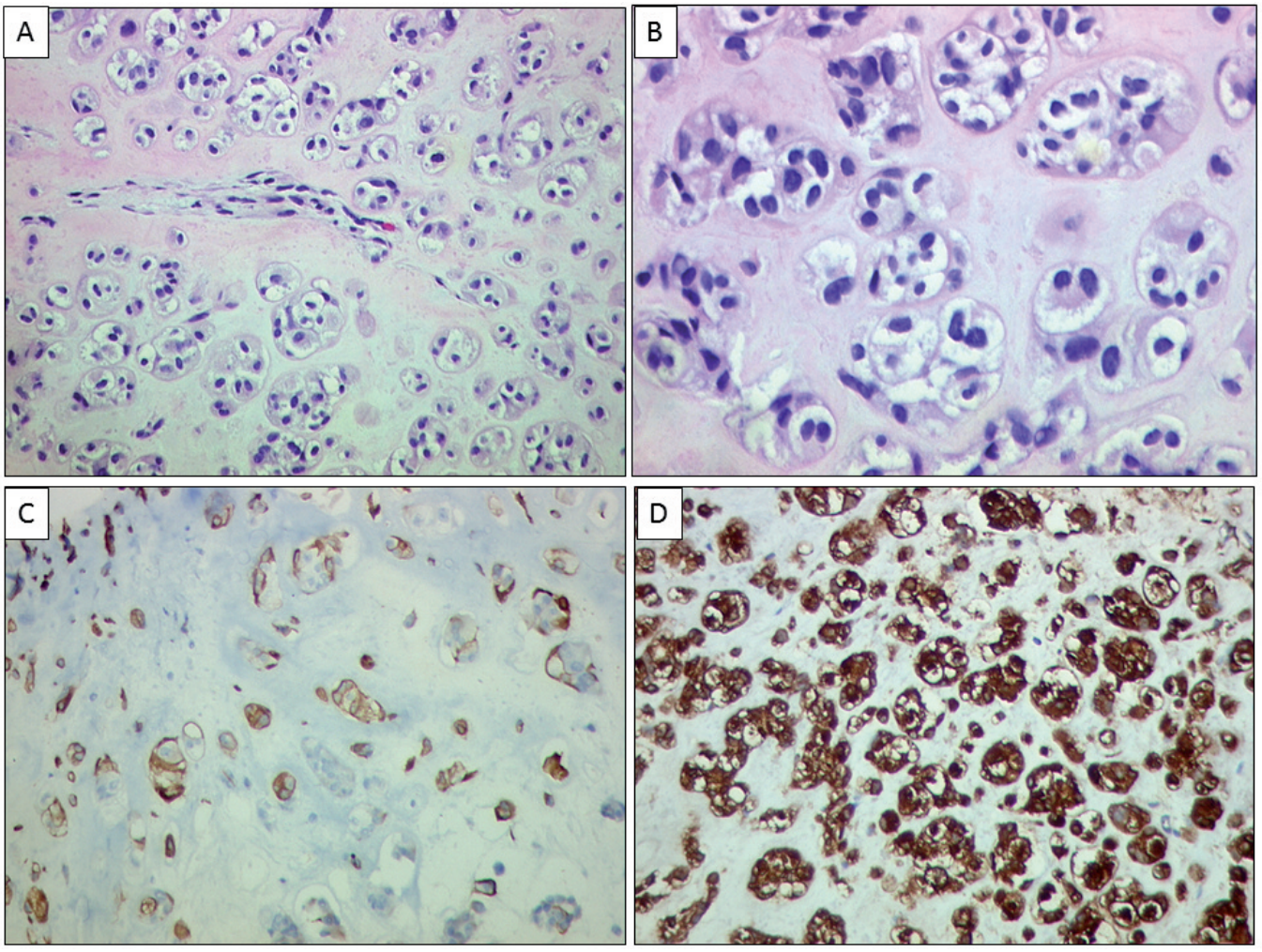

Fig. 6. Myepithelial carcinoma. **A.** Tumor composed of cells arranged in small nests within abundant hyaline stroma. **B.** Tumor cells showing moderate nuclear atypia, vacuolated to eosinophilic cytoplasm. H and E. **C.** EMA positivity within tumor cells. DAB. **D.** Diffuse S100 preotein positivity within tumor cells. DAB. A, x 200; B-D, x 400.

considering at least moderate nuclear atypia as the criterion for malignancy. Lately, in another study, Jo and Fletcher (Jo and Fletcher, 2015) reinforced at least moderate degree of nuclear atypia as the criterion for malignancy in METs. Mitotic activity in METs has been found to be variable, irrespective of benign or malignant sub-types (Hornick and Fletcher, 2003). In their study on METs, Hornick and Fletcher (Hornick and Fletcher, 2003) observed mitotic figures ranging from 0 and 68 per 10 high power fields, the average being 4.8. In their study, Rekhi et al. (2012) observed no significant mitotic figures in 5 myoepitheliomas, whereas mitotic figures ranging from 10-50/10 hpf in 9 cases of myoepithelial carcinomas of soft tissues, all accompanied with at least moderate nuclear atypia. Coagulative tumor necrosis is seen more commonly in malignant METs (Rekhi et al., 2016). Heterologous chondrosarcomatous and osteosarcomatous differentiation have also been described in soft tissue METs (Hornick and Fletcher, 2003). While mixed tumors are composed of both epithelial (duct formation/differentiation) and myoepithelial cells in varying proportions, myoepitheliomas and myoepithelial carcinomas comprise cells lacking ductal differentiation (Kilpatrick et al., 1997; Hornick and Fletcher, 2003). Most cases of malignancy occur *de novo*. Rarely, malignant METs arise from a pre-existing myoepithelioma (Hornick and Fletcher, 2003) (Figs. 2-10A).

Genetic aberrations

Recent studies have unraveled certain genetic aberrations underlying METs of soft tissue and bone, including *EWSR1* gene rearrangement as the commonest genetic alteration, noted in approximately 45-50% of the

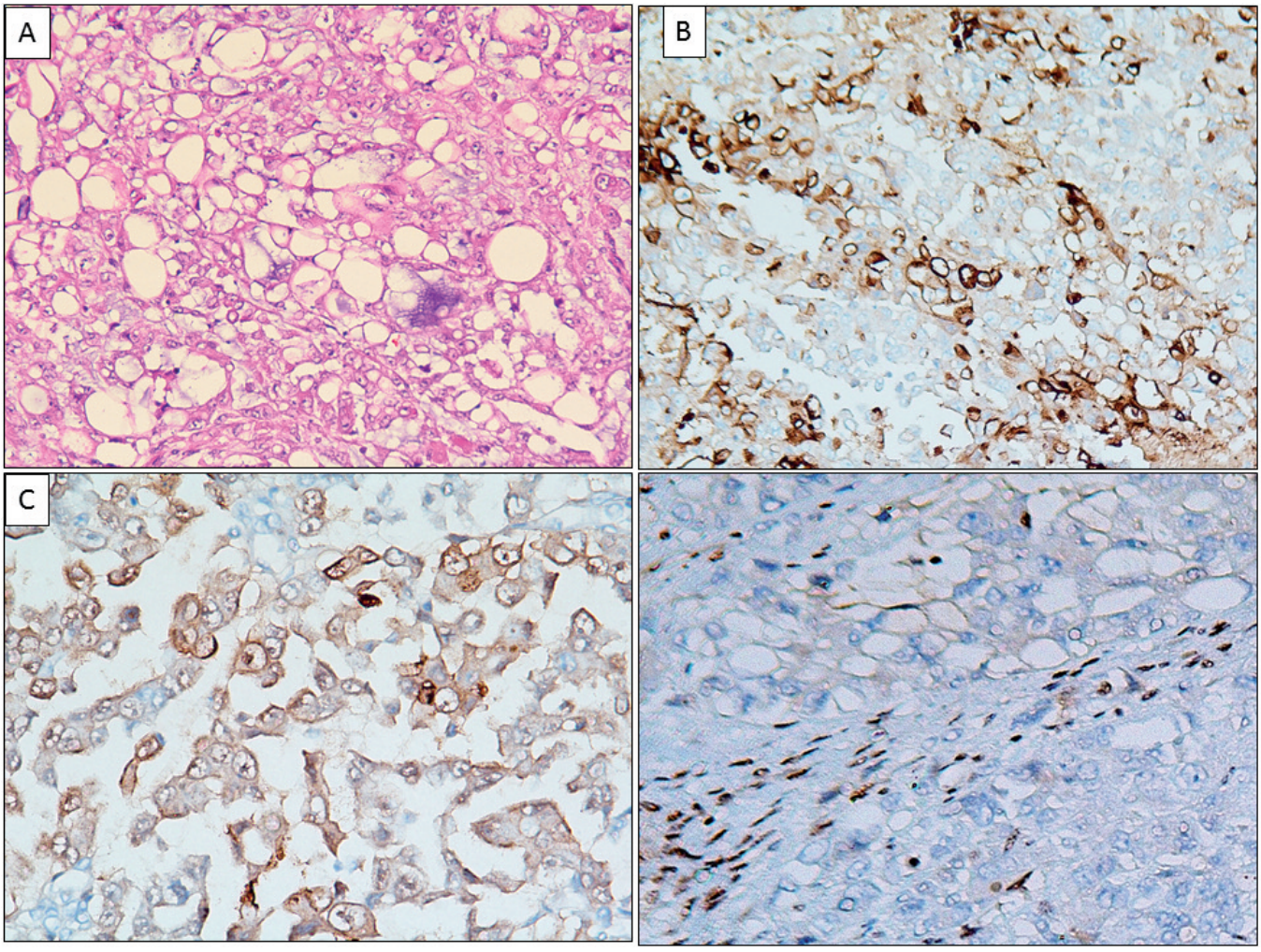

Fig. 7. A. A case of a myoepithelial tumor composed of cells with prominent cytoplasmic vacuolation and focal myxoid stroma, indicative of a parachordoma. H and E. **B.** Tumor cells displaying EMA positivity. DAB. **C.** Tumor cells displaying focal S100 protein positivity. **D.** Tumor cells displaying complete loss of INI1. Interveing lymphocytes and endothelial cells acting as internal positive control. DAB. x 400.

these tumors (Antonescu et al., 2010; Flucke et al., 2011; Rekhi et al., 2012, 2016) (Fig. 10B). Brandal et al. (2008, 2009) reported *EWSR1-PBX1* and *EWSR1-ZNF444* fusion transcripts in a single case, each of a myoepithelioma and a myoepithelial carcinoma, respectively. Subsequently, Antonescu et al. (2010) demonstrated that *EWSR1* rearrangement was consistently present in METs albeit with various partner genes. They observed *EWSR1* rearrangement with some of the partner genes associated with specific histopathologic features. In their study, mixed tumors did not show *EWSR1* gene rearrangement (Antonescu et al., 2010). Kurzawa et al. (2013) identified *EWSR1* gene rearrangement in 71% cases of intraosseous myoepithelioma. Antonescu et al. (2010) observed *EWSR1* rearrangement in 50% malignant METs and in 40% benign METs, mostly in deep-seated tumors. In the same study, among the cases showing *EWSR1* rearrangement, 53% of cases were malignant and 47% were benign. Rekhi et al. (2012, 2016) identified *EWSR1* rearrangement in 3/6 soft tissue METs and in a single case of an intraosseous myoepithelial carcinoma, where this was tested. Flucke et al. (2011) identified *EWSR1* rearran-gement in 44% cases of cutaneous METs. They observed *EWSR1* rearrangement in myoepitheliomas, as well as in mixed tumors (Flucke et al., 2011). Contrastingly, Bahrami et al (Bahrami et al., 2012) did not identify *EWSR1* rearrangement in mixed tumors.

Fusion with specific partner genes, such as *POU5F1* and *PBX1* has been reported in 16% METs that show *EWSR1* rearrangement (Antonescu et al., 2010). *PBX3, ZNF444, ATF1, KLF17, NFATC2* are uncommon genes forming specific transcripts, underlying certain METs (Antonescu et al., 2010; Flucke et al., 2012a,b; Romeo et

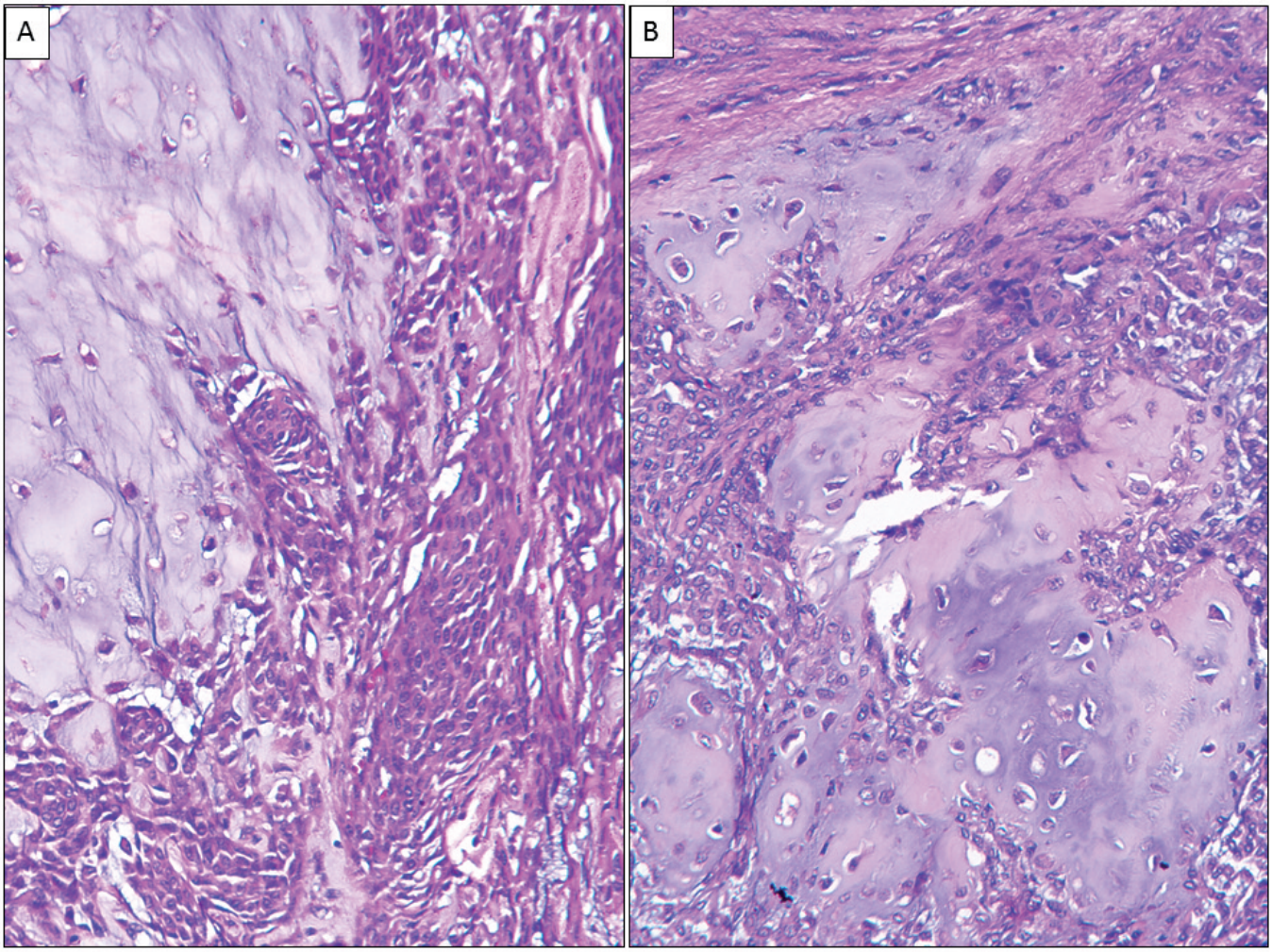

Fig. 8. Introassoeus myepithelial carcinoma. Microscopic findings. **A.** Tumor composed of cells exhibiting moderate nuclear atypia, arranged in sheets and cords and displaying squmaous differentiation, with areas of prominent chondroid differentiation. H and E. **B.** Conspicuous areas of chondroid differentiation. H and E. x 200.

al., 2012; Agaram et al., 2015; Huang et al., 2015). In certain cases of METs, the partner genes have not yet been identified. Antonescu et al. (2010) observed that tumors showing *EWSR1-POU5F1* fusion are seen in young patients (mean 21 years; median 26 years). These tend to be situated in relatively deeper locations, are more commonly malignant and have a nested arrangement of clear cells. They also observed that tumors with *EWSR1-PBX1* fusion are seen in middle-aged patients (mean 46 years); in deep soft tissues, bones and visceral organs and could be either benign or malignant. These tumors show spindle and epithelioid cells in a sclerotic and fibrotic stroma. In a recent study, Agaram et al. (2015), observed *EWSR1-PBX3* mutation more frequently in the bones. Histopathologically, these tumors tend to show epithelioid to oval cells, embedded within a sclerotic or myxoid stroma (Agaram et al., 2015). ECT of the tongue is reported to show *EWSR1* rearrangement in 25% of cases, further reinforcing its genetic link with a MET (Argyris et al., 2016).

Nearly 9% of METs that do not show *EWSR1* gene rearrangement are characterized by *FUS* gene rearrangement. *KLF17* and *POU5F1* constitute as the only known fusion partners for *EWSR1* gene in these cases. In a recent study, *KLF17* fusion was seen in 66% cases of *FUS* rearranged METs. Such tumors tend to occur in young patients (mean 28 years; median 32years) and have a male preponderance. Although soft tissues are predominantly involved, these tumors are also known to occur in the bones and visceral organs. Histopathologically, these METs are more frequently benign than malignant and show the entire morphologic spectrum known in METs (Huang et al., 2015). *FUS-POU5F1* fusion transcript has been reported in a single case of an intraosseous myoepithelioma (Puls et al., 2014). In another case report of a large intraosseous myo-

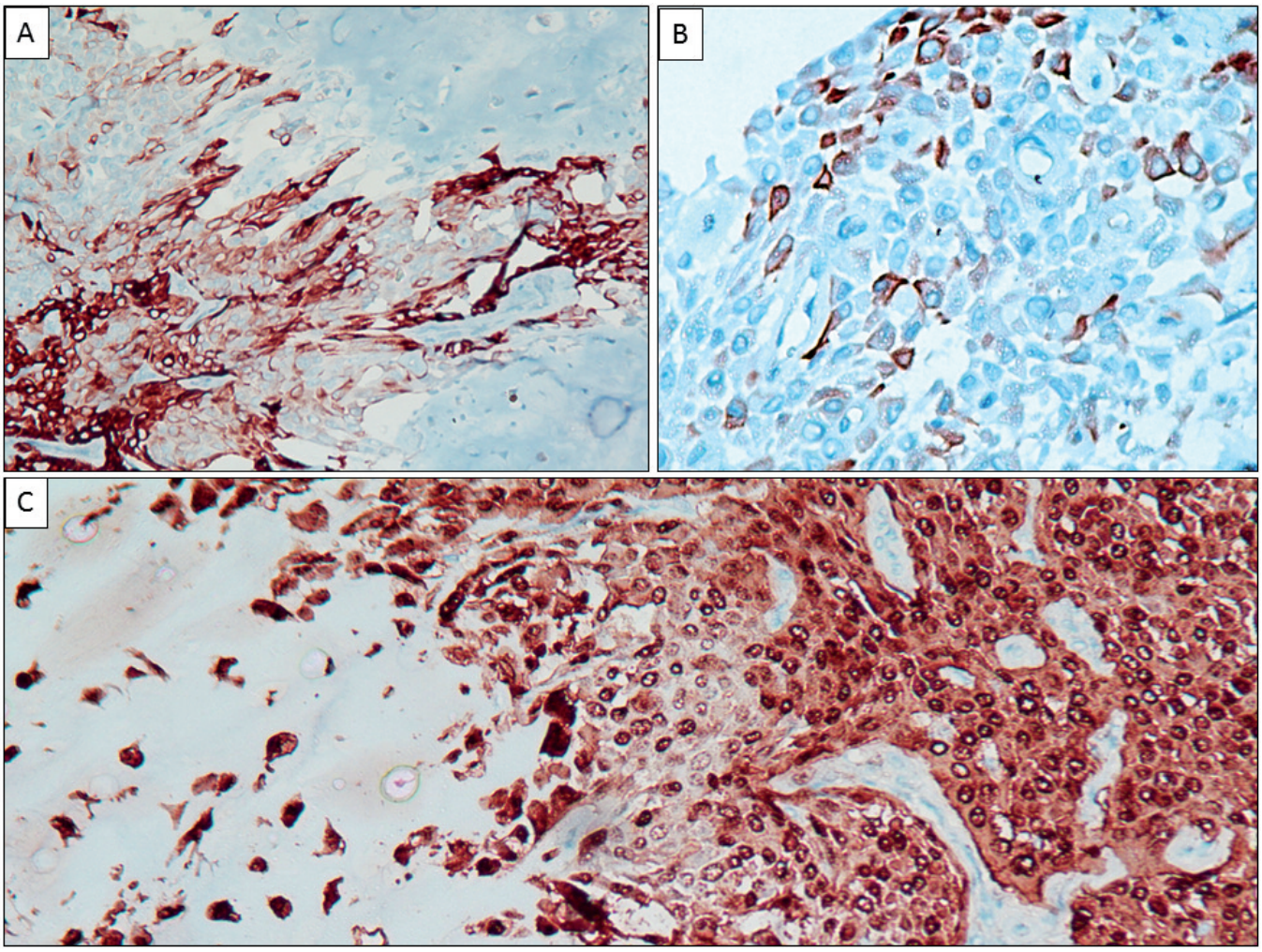

Fig. 9. Immunohistochemical findings. **A**. Tumor cells displaying CK7 positivity. DAB. **B.** Tumor cells showing distinct, focal GFAP positivity. DAB. **C.** Tumor cells showing diffuse S100 protein positivity. DAB. x 400.

epithelioma, displaying promineent squamous metaplasia, *EWSR1* rearrangment was absent. The same tumor displayed trisomies of chromosomes 11, 15 and 17 and del (16q) and del (22q11) (Rekhi et al., 2011).

PLAG1 gene rearrangement is reported in pleomorphic adenoma of the salivary gland (Martins et al., 2005). METs lacking *EWSR1* and *FUS* gene rearrangement have been found to show *PLAG1* gene rearrangement in 37% cases. These METs present as superficial, as well as deep-seated lesions. Almost all such tumors show tubulo-ductular differentiation (mixed tumors). It is noteworthy that a gene rearrangement can be seen in the form of a balanced translocation, an unbalanced translocation, inversion and interstitial deletion (Bahrami et al., 2012; Antonescu et al., 2013). *LIFR-PLAG1* gene fusion has been reported in a single case of a MET (Antonescu et al., 2013). *PLAG1* gene fusions with *CTNNB1, FGFR1* and *HMGA2* genes, observed in mixed salivary gland tumors, have not been reported in METs of bone and soft tissues. However, a single case of a MET showing an increased copy number of *HMGA2* has been reported. An ECT lacks *PLAG1* mutation (Antonescu et al., 2013).

The value of molecular testing lays in differentiating an MET from its differential diagnoses. EMC, one of the closest differentials of a MET also shows *EWSR1* gene rearrangement, but the fusion partner in cases of EMC is *NR4A3*. In a documented study, all cases of EMC showed fusion of *NR4A3* gene, either with *EWSR1* gene, or with other genes (Flucke et al., 2012a,b). In cases of equivocal features, molecular tests can be used to differentiate a MET from an OFMT. OFMTs show *PHF1* gene rearrangement in 80% cases and lack *EWSR1* rearrangement (Jo, 2015). Adamantinoma-like EFTs also display

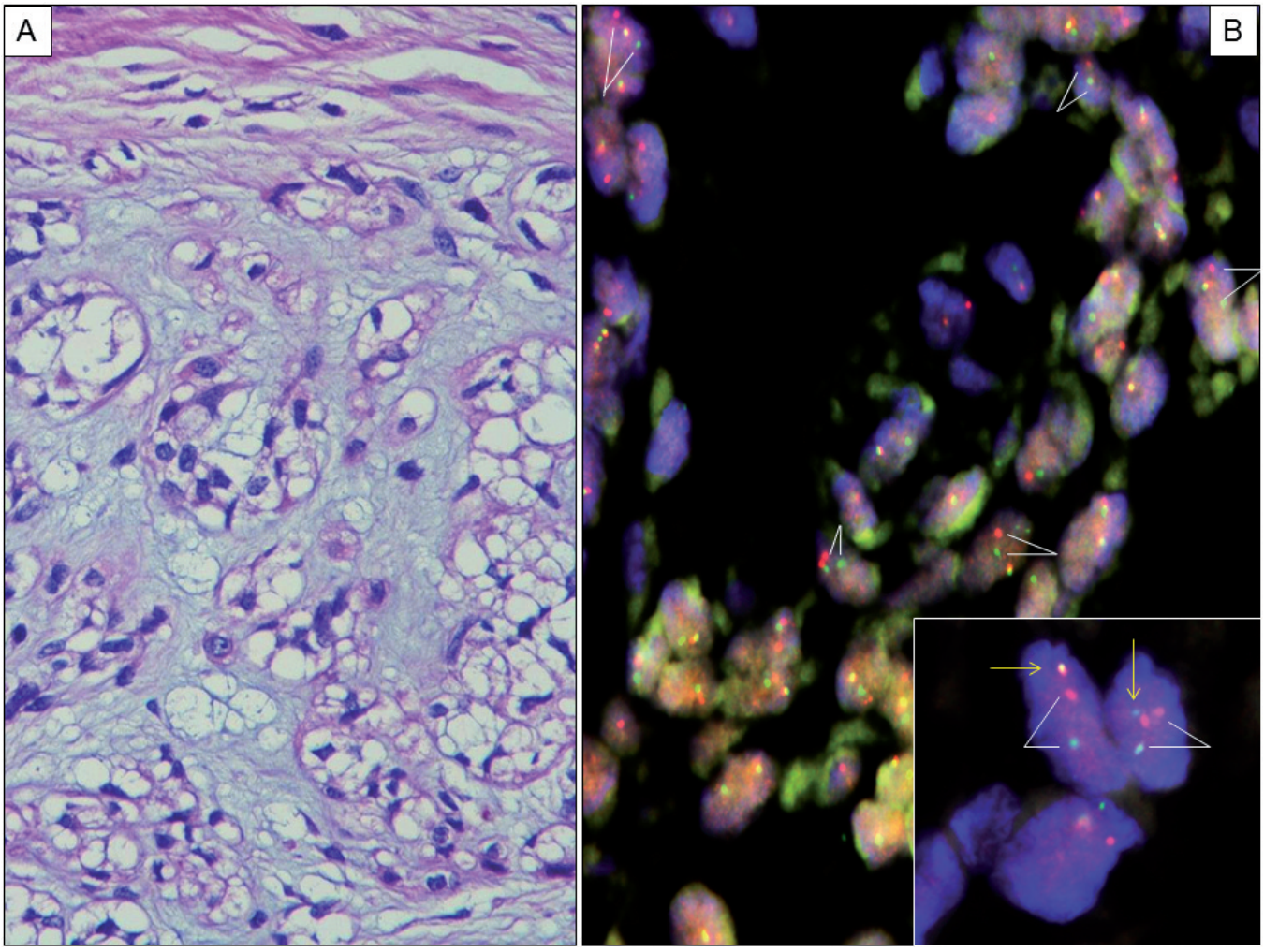

Fig. 10. A. Parachordoma. H and E. **B.** Fluorescent in-situ hybridization technique displaying EWSR1 rearrangement. Double lines show 'split' orange/green signals, indicative of rearrangement. DAP. Inset displaing 'split' orange/green signals (double arrows) along with single fused signal (yellow arrow), indicative of EWSR1 rearrangement. DAPI. A, x 400; B, inset, x 1,000.

EWSR1 rearrangement, but the fusion partner is *FLI1* in those cases (Table 1, Fig. 11) (Bishop et al., 2015).

Differential diagnoses

Several differential diagnoses need to be considered before making diagnosis of a MET. Metastatic tumors, especially malignant mixed epithelial tumors and myoepithelial carcinomas from the salivary gland need to be excluded by clinico-radiologic examination. Metastasis of tumors, such as mucinous adenocarcinomas can be ruled out with the help of positive IHC expression of S100 protein and GFAP that is seen in METs (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007).

An extraskeletal myxoid chondrosarcoma (EMC) shows overlapping histopathologic features with a MET. By immunohistochemistry, EMCs are generally negative for cytokeratins, unlike METs, but do express S100 protein and EMA, similar to METs (Hornick and Fletcher, 2003; Gleason and Fletcher, 2007; Kurzawa et al., 2013). In such cases, molecular testing is recommended.

An Ossifying fibromyxoid tumor (OFMT) also shows overlapping histopathologic and IHC features with a MET. However, in contrast to a MET, an OFMT invariably shows monomorphic oval cells with a peripheral rim of ossification. The intervening stroma in an OFMT is invariably myxoid, in contrast to a relatively more variable stroma within cells of a MET, ranging from dense hyaline-like (as noted in a sclerosing epithelioid fibrosarcoma), to chondroid to an osseous type. There is a considerable overlap of expression of IHC markers between an OFMT and a MET. In difficult cases, particularly in "non-ossifying" variant of an OFMTs, the molecular tests are useful (Hornick and Fletcher, 2003; Antonescu et al., 2010). A sclerosing rhabdomyosarcoma can be differentiated from a MET, based on positive expression of muscle specific markers, such as desmin, along with skeletal muscle specific markers, such as MyoD1 and myogenin.

Considering 40% cases of MET display loss of SMARCB1/INI1, various tumor entities showing loss of INI1 constitute as differential diagnoses of a MET, for

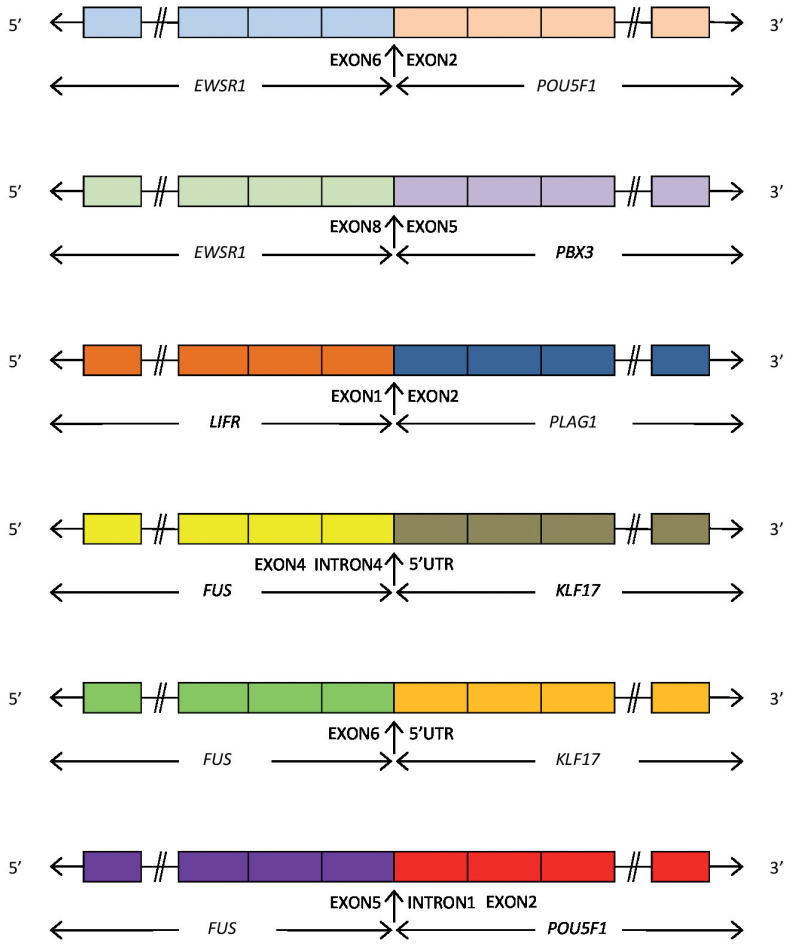

Fig. 11. Schematic representation of various fusion transcripts underlying myoepithelial tumors of soft tissues.

example, an extra-renal rhabdoid tumor (ERRT) in pediatric patients and an epithelioid sarcoma. Immunoexpression of INI1 is invariably lost, while expression of S100 protein is variable in an ERRT (Gleason and Fletcher, 2007; Agaram et al., 2015). Similarly, epithelioid sarcomas (ESs) do not express S100 protein in a substantial number of tumor cells. Moreover, in nearly 60-70% cases of ES, CD34 is positive (Hornick and Fletcher, 2003; Agaram et al., 2015). An epithelioid malignant peripheral nerve sheath tumor displays overlapping histopathologic features, IHC profile, including positivity for epithelial markers and S100 protein, as well as loss of INI1 in certain cases. The presence of a variable amount of chondromyxoid stroma is more commonly seen in a MET. Furthermore, molecular testing is recommended, considering METs display specific molecular signatures that are lacking in an epithelioid MPNST.

Various differential diagnoses of an intraosseous MET, include a chondromyxoid fibroma; an adamantinoma; a chondrosarcoma, to an osteosarcoma with chondroblastic differetiation (Rekhi et al., 2011, 2016).

A chondromyxoid fibroma, an osteosarcoma and a chondrosarcoma can be differentiated from a MET, based on negative expression of epithelial IHC markers in these tumors, in contrast to a MET (Kurzawa et al., 2013). Squamous differentiation, reported within intraosseous METs, is characteristically seen in an adamantinoma, including its dedifferentiated subtype (Hazelbag et al., 2003; Kanamori and Hogendoorn, 2013; Bishop et al., 2015). In such cases, positive expression of S100 protein and GFAP are crucial in confirmation of a MET, over an adamantinoma (Rekhi et al., 2011, 2016).

An abaxial chordoma needs exclusion in cases where vacuolated cells predominate, for example a parachordoma. S100 protein and epithelial markers are similarly expressed by chordomas. However, brachyury, which is a highly specific and a sensitive for chordomas, is consistently negative in METs (Jo, 2015; Rekhi et al., 2016). "Adamantinoma-like" Ewing family tumors (EFT) show uniformly arranged small round cells and might resemble a myoepithelial carcinoma (Bishop et al., 2015). These tumors show positive expression of S100 protein and actin as well. Besides overlapping histopathologic and IHC features, these two tumors

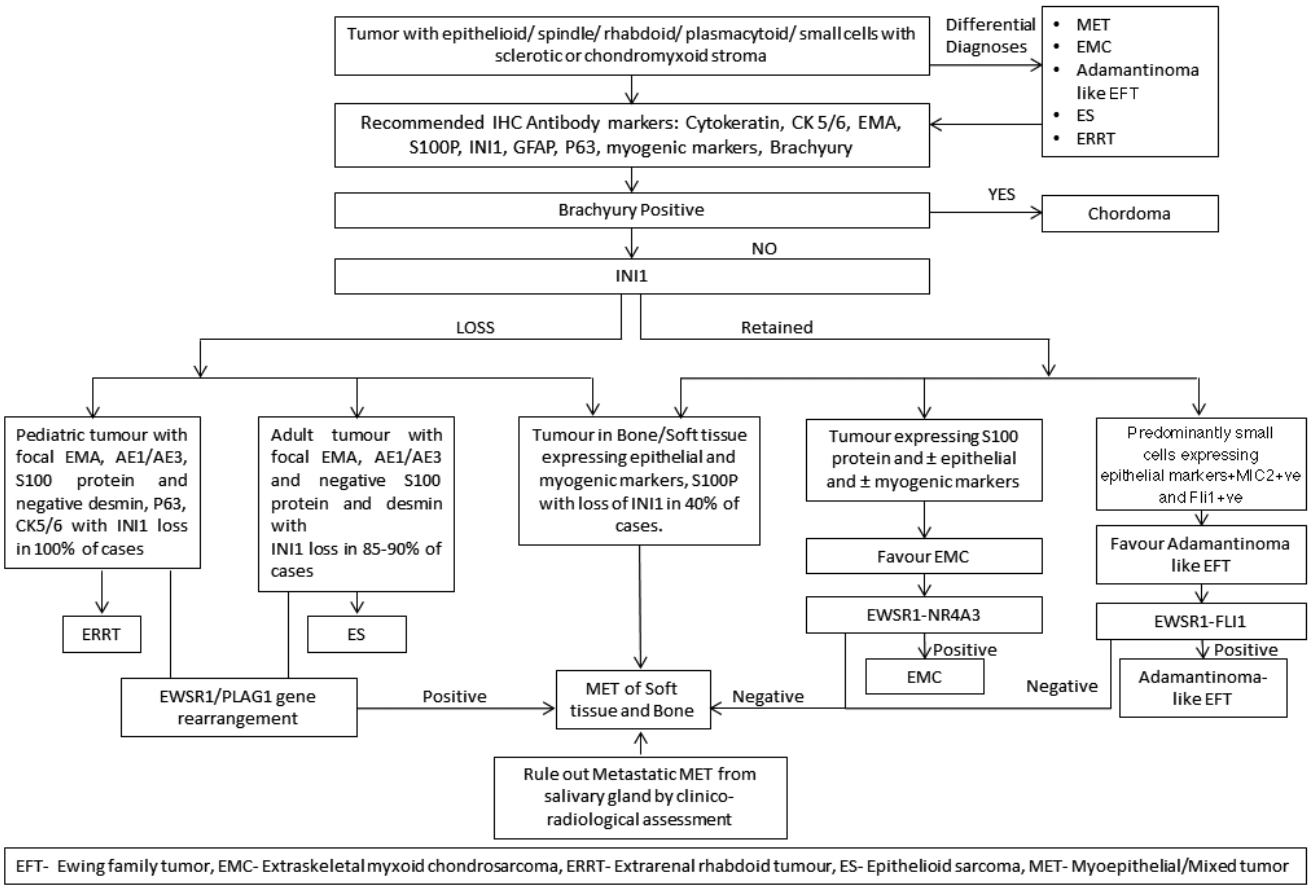

Fig. 12. Flow chart depicting approach to diagnosis of Myoepithelial tumors of Bone and Soft tissue.

show similar molecular features, including *EWSR1* rearrangement (Fig. 12) (Antonescu et al., 2010; Flucke et al., 2011; Rekhi et al., 2012; Bishop et al., 2015). However, the fusion partner genes are different.

Treatment and outcomes

Diagnosis of a MET has significant treatment implications. Surgical resection with clear margins remains the preferred treatment for choice of METs, irrespective of benign or malignant subtypes. Adjuvant radiation therapy may be offered in cases with marginal or intracapsular resections for a better loco-regional clearance. The role of chemotherapy is unclear (Rekhi et al., 2012, 2016; Domingo-Musibay et al., 2016). This is in contrast to certain diagnostic mimics of METs, such as a metastatic adenocarcinoma, where a specific chemotherpay might be offered, as well as a conventional high-grade osteosarcoma that is treated with a specific chemotherapy in neoadjuvant settings.

Chances of recurrences in cases of benign METs range from 18% to 29%, while in malignant METs, these are between 42% and 64% (Hornick and Fletcher, 2003; Domingo-Musibay et al., 2016). In a recently published retrospective clinical analysis, Domingo-Musibay et al (Domingo-Musibay et al., 2016), reported 5-year event free survival rates of 88% and 36%, in low-grade and high-grade METs, respectively. The low-grade and high grade METs in their study were equivalent to benign and malignant METs, respectively (Hornick and Fletcher, 2003; Domingo-Musibay et al., 2016). In an earlier study, metastasis and death was recorded in 32% and 13%, respectively, in cases of malignant METs (Hornick and Fletcher, 2003). Metastasis is more commonly seen in pediatric patients (Gleason and Fletcher, 2007; Domingo-Musibay et al., 2016). Gleason et al (Gleason and Fletcher, 2007) documented metastasis in 52% cases of pediatric myoepithelial carcinomas, while Domingo-Musibay et al. (Domingo-Musibay et al., 2016) observed metastasis in 43% cases of adult myoepithelial carcinomas. Multiple recurrences can be seen in both benign and malignant tumors. Recurrence is more common in patients undergoing marginal excisions, as compared to patients undergoing wide-excisions (Gleason and Fletcher, 2007). METs can metastasize to the regional lymph nodes, or to distant organs, most commonly lungs, along with other sites, such as bones, mediastinum, spine, orbit, soft tissues and brain (Hornick and Fletcher, 2003). Tumor size more than, equal to 5 cm and tumor necrosis are important prognostic markers (Gleason and Fletcher, 2007).

Histogenesis of these tumors, especially intraosseous METs is unclear. Presently METs of soft tissue and bone are included in the category of tumors with uncertain histogenesis. One of the possible hypotheses is displacement of myoepithelial elements during embryogenesis into deeper soft tissues and bones, where these tumors originate (de Pinieux et al., 2001; Rekhi et al., 2011, 2012, 2016). There is an increasing evidence that epithelial and myoepithelial cell populations share phenotypic and genotypic characteristics, supporting the concept of a modified myoepithelial cell model. Probably, a single pluripotent cell is capable of differentiating into a variety of morphologic/phenotypic forms (Antonescu et al., 2013).

Conclusions

A MET of soft tissue and bone and is a distinct tumor entity, which is diagnosed with the help of certain histopathologic features, combined with IHC results. METs show a wide range of histopathologic features including various cell types, architectural patterns and stroma, leading to a range of differential diagnoses. Co-expression of epithelial IHC markers with S100 protein and or GFAP immunoreactivity along with other optional IHC markers is helpful in making an accurate diagnosis of a MET. Certain METs show loss of SMARCB1/INI1 protein. METs, including a parachordoma are different from an extra axial chordoma or chordoma peripheric um, based on brachyury negativity within METs, in contrast to chordomas. Presently, moderate nuclear atypia constitutes as the criterion for malignancy in cases of MET of bone and soft tissues. *EWSR1, FUS* and *PLAG1* gene rearrangements, leading to formation of specific fusion transcripts, are noted in a subset of METs, constituting as their molecular 'signatures', associated with certain specific clinicopathologic features. In certain cases where differential diagnoses canot be resolved with IHC, molecular testing is recommended. A correct diagnosis has treatment implications. Surgical resection, preferably with clear margins is a definitive treatment, irrespective of a benign or a malignant MET. Adjuvant radiation therapy following excision may be offered in recurrent and malignant cases. The role of chemotherapy is unclear. A malignant or a high-grade MET is associated with a significantly more aggressive clinical course than a benign or a low-grade MET.

References

Agaram N.P., Chen H.W., Zhang L., Sung Y.S., Panicek D., Healey J.H., Nielsen G.P., Fletcher C.D. and Antonescu C.R. (2015). EWSR1-PBX3: a novel gene fusion in myoepithelial tumors. Genes Chromosomes Cancer 54, 63-71.

Antonescu C.R., Zhang L., Shao S.Y., Mosquera J.M., Weinreb I., Katabi N. and Fletcher C.D. (2013). Frequent PLAG1 gene rearrangements in skin and soft tissue myoepithelioma with ductal differentiation. Genes Chromosomes Cancer 52, 675-682.

Antonescu C.R., Zhang L., Chang N.E., Pawel B.R., Travis W., Katabi N., Edelman M., Rosenberg A.E., Nielsen G.P., Dal Cin P. and Fletcher C.D. (2010). EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. Genes Chromosomes Cancer 49, 1114-1124.

Argyris P.P., Bilodeau E.A., Yancoskie A.E., Trochesset D.,

Pambuccian S.E., Wetzel S.L., Shah S.S., Edelman M., Freedman P., Dolan M. and Koutlas I.G. (2016). A subset of ectomesenchymal chondromyxoid tumors of the tongue shows EWSR1 rearrangements and is genetically linked to soft tissue myoepithelial neoplasms: A study of 11 cases. Histopathology 69, 607-613.

Bahrami A., Dalton J.D., Krane J.F. and Fletcher C.D. (2012). A subset of cutaneous and soft tissue mixed tumors are genetically linked to their salivary gland counterpart. Genes Chromosomes Cancer 51, 140-148.

Bishop J.A., Alaggio R., Zhang L., Seethala R.R. and Antonescu C.R. (2015). Adamantinoma-like Ewing family tumors of the head and neck: a pitfall in the differential diagnosis of basaloid and myoepithelial carcinomas. Am. J. Surg. Pathol. 39, 1267-1274.

Brandal P., Panagopoulos I., Bjerkehagen B. and Heim S. (2009). t(19;22)(q13;q12) Translocation leading to the novel fusion gene EWSR1-ZNF444 in soft tissue myoepithelial carcinoma. Genes Chromosomes Cancer 48, 1051-1056.

Brandal P., Panagopoulos I., Bjerkehagen B., Gorunova L., Skjeldal S., Micci F. and Heim S. (2008). Detection of a t(1;22)(q23;q12) translocation leading to an EWSR1-PBX1 fusion gene in a myoepithelioma. Genes Chromosomes Cancer 47, 558-564.

Burke T., Sahin A., Johnson D.E., Ordonez N.G. and Mackay B. (1995). Myoepithelioma of the retroperitoneum. Ultrastruct. Pathol. 19, 269-274.

Dabska M. (1977). Parachordoma: a new clinicopathologic entity. Cancer 40, 1586-1592.

de Pinieux G., Beabout J.W., Unni K.K. and Sim F.H. (2001). Primary mixed tumor of bone. Skeletal Radiol. 30, 534-536.

Domingo-Musibay E., Oliveira A.M., Okuno S.H., Petersen I.A., Rose P.S. and Robinson S.I. (2016). Myoepithelioma of soft tissues: A single institution retrospective case series. Am. J. Clin. Oncol. [Epub ahead of print].

Fisher C. and Miettinen M. (1997). Parachordoma: a clinicopathologic and immunohistochemical study of four cases of an unusual soft tissue neoplasm. Ann. Diagn. Pathol. 1, 3-10.

Fletcher C.D., Antonescu C.R., Heim S. and Hornick J.L. (2013). Myoepithelioma/myoepithelial carcinoma/mixed tumor. In: World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone, Fletcher C.D., Bridge J.A., Hogendoorn P.C. and Mertens F. (eds). IARC Press. Lyon, France. pp 208-209.

Flucke U., Palmedo G., Blankenhorn N., Slootweg P.J., Kutzner H. and Mentzel T. (2011). EWSR1 gene rearrangement occurs in a subset of cutaneous myoepithelial tumors: a study of 18 cases. Mod. Pathol. 24, 1444-1450.

Flucke U., Mentzel T., Verdijk M.A., Slootweg P.J., Creytens D.H., Suurmeijer A.J. and Tops B.B. (2012a). EWSR1-ATF1 chimeric transcript in a myoepithelial tumor of soft tissue: a case report. Hum. Pathol. 43, 764-768.

Flucke U., Tops B.B., Verdijk M.A., van Cleef P.J., van Zwam P.H., Slootweg P.J., Bovee J.V., Riedl R.G., Creytens D.H., Suurmeijer A.J. and Mentzel T. (2012b). NR4A3 rearrangement reliably distinguishes between the clinicopathologically overlapping entities myoepithelial carcinoma of soft tissue and cellular extraskeletal myxoid chondrosarcoma. Virchows Arch. 460, 621-628.

Gleason B.C. and Fletcher C.D. (2007). Myoepithelial carcinoma of soft tissue in children: an aggressive neoplasm analyzed in a series of 29 cases. Am. J. Surg. Pathol. 31, 1813-1824.

Hazelbag H.M., Laforga J.B., Roels H.J. and Hogendoorn P.C. (2003). Dedifferentiated adamantinoma with revertant mesenchymal phenotype. Am. J. Surg. Pathol. 27, 1530-1537.

Hornick J.L. and Fletcher C.D. (2003). Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am. J. Surg. Pathol. 27, 1183-1196.

Huang S.C., Chen H.W., Zhang L., Sung Y.S., Agaram N.P., Davis M., Edelman M., Fletcher C.D. and Antonescu C.R. (2015). Novel FUS-KLF17 and EWSR1-KLF17 fusions in myoepithelial tumors. Genes Chromosomes Cancer 54, 267-275.

Jo V.Y. (2015). Myoepithelial tumors: An update. Surg Pathol Clin 8, 445-466.

Jo V.Y. and Fletcher C.D. (2015). Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. Head Neck Pathol. 9, 32-38.

Kanamori M. and Hogendoorn P.C.W. (2013). Adamantinoma. In: World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone, Fletcher C.D., Bridge J.A., Hogendoorn P.C. and Mertens F. (eds). IARC Press. Lyon, France. pp 343-345.

Kilpatrick S.E., Hitchcock M.G., Kraus M.D., Calonje E. and Fletcher C.D. (1997). Mixed tumors and myoepitheliomas of soft tissue: a clinicopathologic study of 19 cases with a unifying concept. Am. J. Surg. Pathol. 21, 13-22.

Kurzawa P., Kattapuram S., Hornicek F.J., Antonescu C.R., Rosenberg A.E. and Nielsen G.P. (2013). Primary myoepithelioma of bone: a report of 8 cases. Am. J. Surg. Pathol. 37, 960-968.

Martins C., Fonseca I., Roque L., Pereira T., Ribeiro C., Bullerdiek J. and Soares J. (2005). PLAG1 gene alterations in salivary gland pleomorphic adenoma and carcinoma ex-pleomorphic adenoma: a combined study using chromosome banding, in situ hybridization and immunocytochemistry. Mod. Pathol. 18, 1048-1055.

Michal M. and Miettinen M. (1999). Myoepitheliomas of the skin and soft tissues. Report of 12 cases. Virchows Arch. 434, 393-400.

Miettinen M., McCue P.A., Sarlomo-Rikala M., Biernat W., Czapiewski P., Kopczynski J., Thompson L.D., Lasota J., Wang Z. and Fetsch J.F. (2015). Sox10--a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue: a systematic analysis of 5134 tumors. Am. J. Surg. Pathol. 39, 826-835.

Puls F., Arbajian E., Magnusson L., Douis H., Kindblom L.G. and Mertens F. (2014). Myoepithelioma of bone with a novel FUS-POU5F1 fusion gene. Histopathology 65, 917-922.

Rekhi B., Amare P., Gulia A., Baisane C., Patil A., Agarwal S., Puri A. and Jambhekar N.A. (2011). Primary intraosseous myoepithelioma arising in the iliac bone and displaying trisomies of 11, 15, 17 with del (16q) and del (22q11)--A rare case report with review of literature. Pathol. Res. Pract. 207, 780-785.

Rekhi B., Sable M. and Jambhekar N.A. (2012). Histopathological, immunohistochemical and molecular spectrum of myoepithelial tumours of soft tissues. Virchows Arch. 461, 687-697.

Rekhi B., Desai S.S., Gulia A., Puri A. and Jambhekar N.A. (2014). Intraosseous myoepithelioma: a rare, distinct tumor entity. Indian J. Pathol. Microbiol. 57, 269-271.

Rekhi B., Joshi S., Panchwagh Y., Gulia A., Borges A., Bajpai J., Jambehekar N.A., Pant V., Mandholkar M., Byregowda S. and Puri A. (2016). Clinicopathological features of five unusual cases of intraosseous myoepithelial carcinomas, mimicking conventional primary bone tumours, including EWSR1 rearrangement in one case. APMIS 124, 278-290.

Romeo S., Bovee J.V., Kroon H.M., Tirabosco R., Natali C., Zanatta L., Sciot R., Mertens F., Athanasou N., Alberghini M., Szuhai K.,

Hogendoorn P.C. and Dei Tos A.P. (2012). Malignant fibrous histiocytoma and fibrosarcoma of bone: a re-assessment in the light of currently employed morphological, immunohistochemical and molecular approaches. Virchows Arch. 461, 561-570.

Savera A.T., Sloman A., Huvos A.G. and Klimstra D.S. (2000). Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 patients. Am. J. Surg. Pathol. 24, 761-774.

Shin H.J., Mackay B., Ichinose H., Ayala A.G. and Romsdahl M.M. (1994). Parachordoma. Ultrastruct. Pathol. 18, 249-256.

Smith B.C., Ellis G.L., Meis-Kindblom J.M. and Williams S.B. (1995). Ectomesenchymal chondromyxoid tumor of the anterior tongue. Nineteen cases of a new clinicopathologic entity. Am. J. Surg. Pathol. 19, 519-530.

Tirabosco R., Mangham D.C., Rosenberg A.E., Vujovic S., Bousdras K., Pizzolitto S., De Maglio G., den Bakker M.A., Di Francesco L., Kalil R.K., Athanasou N.A., O'Donnell P., McCarthy E.F. and Flanagan A.M. (2008). Brachyury expression in extra-axial skeletal and soft tissue chordomas: a marker that distinguishes chordoma from mixed tumor/myoepithelioma/parachordoma in soft tissue. Am. J. Surg. Pathol. 32, 572-580.

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