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Case report

Primary intrafascial desmoplastic melanoma with pseudoglandular differentiation and aberrant cytokeratins expression: An exceptional presentation

Andrea Saggini[a,b,*], Lorenzo Cerroni[b], Beatrice Casini[c], Francesca Baciorri[a], Carlo Cota[d]

[a] Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, 00133, Italy
[b] Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, 8036, Austria
[c] Pathology, IRCCS Regina Elena, National Cancer Institute, Rome, 00144, Italy
[d] Department of Dermatology, IRCCS INRCA, Ancona, 60121, Italy

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ABSTRACT

Desmoplastic melanoma (DM) is an uncommon variant of malignant melanoma (MM), histologically characterized by a mainly dermal proliferation of spindled cells within a desmoplastic stroma. Normally, involvement of deeper tissues by DM is the result of direct extension down from the overlying dermis. MM is widely known to harbor a striking potential for morphological and phenotypic variability; among MM morphological variants, pseudoglandular MM is characterized by extensive discohesion within cords and nests of malignant cells and ensuing formation of so-called pseudolumina, thus mimicking adenocarcinoma. We present an exceptional case of DM characterized by intrafascial origin, partly pseudoglandular differentiation, and aberrant experession of cytokeratins in the pseudoglandular component; genetic data from next-generation sequencing supported the final diagnosis of DM, as well as the ontogenetic identity of the pseudoglandular component. Prior to this report, pseudoglandular features had never been described in DM. Additionally, our case is unusual because of the deep origin of the tumor, arising below the subcutaneous fat of the scalp, as well as the aberrant experession of cytokeratins in the pseudoglandular component, thus posing a challenging differential diagnosis with several soft tissue tumors.

1. Introduction

Desmoplastic melanoma (DM) is an uncommon variant of malignant melanoma (MM), histologically characterized by a mainly dermal proliferation of spindled cells in the context of a desmoplastic stroma [1,2]. As a rule, involvement of deeper tissues by DM may be observed only because of direct extension down from the overlying dermis [1–3]; fittingly, DM is thought to arise from a precursor cell within the superficial dermis as a result of the mutagenic effect of chronic sun exposure, consistently with the prominent UV-signature observed in the majority of DM cases [4].

The striking potential of both primary and metastatic MM for morphological and phenotypic variability is widely known [5,6]. Morphologically, MM may show a broad constellation of unusual features at both the cytological and the architectural levels, including pseudoglandular differentiation [5–9]. With the widespread use of immunohistochemistry (IHC), followed by technical improvements in epitope retrieval, the great phenotypic diversity of MM has been progressively discovered [10]; therefore, it has not gone unnoticed that MM may exhibit aberrant expression of non-vimentin intermediate filaments, including cytokeratins [11].

We hereby report the exceptional case of a primary intrafascial DM exhibiting extensive pseudoglandular differentiation coupled with aberrant cytokeratins expression in the pseudoglandular foci; genetic data from next-generation sequencing (NGS) supported the histological diagnosis of DM, as well as the ontogenetic identity of the pseudoglandular component.

2. Case report

A 71-year-old man with no significant medical record presented with a 1-year history of an asymptomatic, slowly growing neoformation localized to the left half of the scalp crown. Upon physical examination, a 4.0 cm × 3.5 cm plaque was observed, covered by normal skin and firm on palpation. No evidence of neurological deficit was detected. An attempt of surgical excision was made.

* Corresponding Author at: Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Viale Oxford 81, 00133, Rome, Italy.
E-mail address: andreasaggini@gmail.com (A. Saggini).

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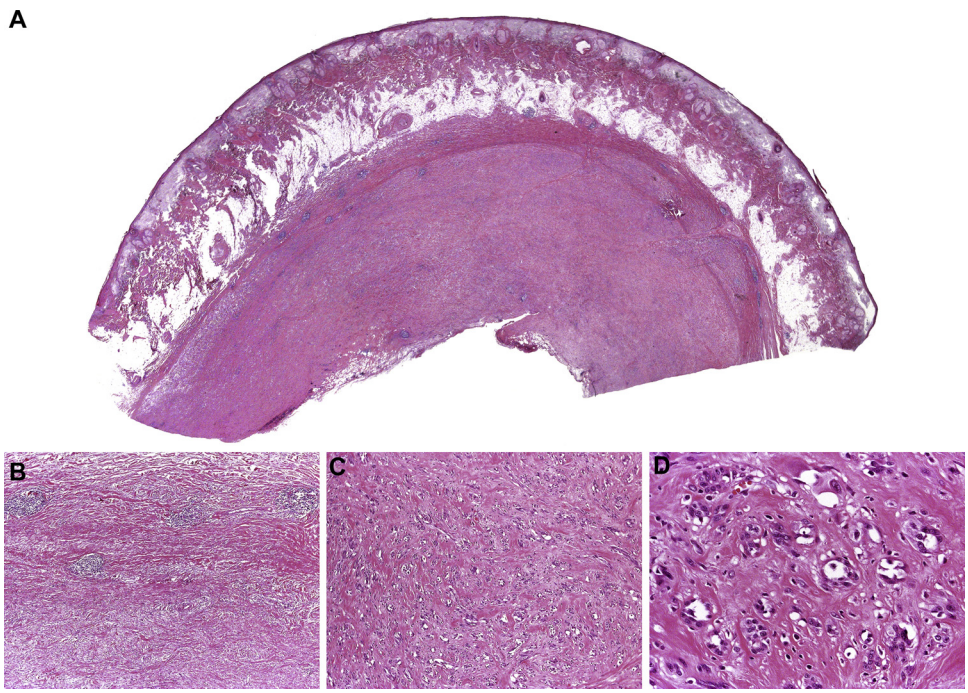

Fig. 1. A, widespread thickening of the scalp superficial fascia due to a desmoplastic, hypocellular neoformation, with extension to the deep margin; the overlying dermis and subcutaneous fat appear to be spared (hematoxylin and eosin, original magnification 2×). **B,** hypocellular proliferation of slender spindled cells arranged in single units within a heavily hyalinized stroma; a patchy lymphoid infiltrate may be noted as well (hematoxylin and eosin, original magnification 4×). **C,** epithelioid cells arranged in nests and cords, surrounded by a desmoplastic stroma; central discohesion within the epithelioid clusters may be observed, resulting in a pseudoglandular morphology (hematoxylin and eosin, original magnification 10×). **D,** higher power view of epithelioid cells, showing eosinophilc cytoplasm, vesicular nuclei, and prominent nucleoli; frequent pseudolumina may be observed as well (hematoxylin and eosin, original magnification 20×).

Histologically, excisional biopsy of the plaque revealed diffuse thickening of the superficial fascia due to a desmoplastic and hypocellular neoformation (Fig. 1A); the neoplastic mass exhibited widespread extension to the lower surgical margin, thus reaching the loose connective tissue layer, while the overlying subcutaneous fat appeared to be spared. With the exception of a diffuse band of solar elastosis in its superficial layer, the dermis appeared unremarkable; careful evaluation of the epidermis revealed only mild actinic melanocytic hyperplasia, with no evidence of any junctional, *in situ* melanocytic proliferation. These findings were confirmed upon extensive sampling of the excisional specimen.

On higher power microscopic examination, the intrafascial desmoplastic tumor exhibited a biphasic pattern. The majority of the neoplasm was characterized by a hypocellular proliferation of slender spindled cells arranged in single units within a heavily hyalinized stroma. Cytological atypia in the spindle-cell population was minimal, with condensed chromatin and unremarkable nucleoli; mitotic activity was scant to absent. Of note, a patchy lymphoid infiltrate, consisting of small lymphocytes and a few plasma cells, could be observed throughout the outward periphery of the tumor, in proximity to the interface between the desmoplastic proliferation and the uninvolved hypodermis (Fig. 1B).

Additionally, several foci with a different histological pattern were noted merging with the spindle-cell proliferation in a haphazard distribution throughout the neoplasm. In these foci, the neoplastic population consisted of polygonal to round epithelioid cells with eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and increased mitotic activity (Fig. 1C). The epithelioid cells appeared to be arranged in nests and cords surrounded by desmoplastic stroma; frequent central discohesion within the epithelioid clusters resulted in formation of lumen-like spaces, thus imparting the appearance of metastatic scirrhous adenocarcinoma (Fig. 1D). Overall, the epithelioid, carcinoma-like cells accounted for approximately 30% of the whole neoplastic population.

On IHC, both the spindled and the epithelioid cell populations were strongly and diffusely positive for S-100 (Figs. 2A and 3 A); intense nuclear expression of SOX-10 (Figs. 2B and 3 B), H3K27me3, and INI-1 mirrored the distribution of S-100 staining. Additionally, the epithelioid component, but not the conventional desmoplastic part, exhibited strong and specific cytoplasmic staining with pan-cytokeratin AE1/AE3 antibody (Figs. 2D, 3 C and D). Staining with other tested antibodies, including Melan-A (Fig. 2C), HMB-45, CAM5.2, CK-7, CK-20, EMA, alpha-SMA, desmin, GFAP, TTF-1, CDX-2, p63, ERG, MyoD1, MUC-4, and TLE-1, was invariably negative in both the two cell populations, with good internal controls when available. No significant nuclear accumulation of p53 protein was noted on IHC. Based on histologic and IHC findings, a diagnosis of primary DM with pseudoglandular differentiation was rendered.

NGS evaluation of the tumor was performed using Ion Torrent next generation sequencing technology [12]. The desmoplastic and pseudoglandular components were manually scraped off from sections of paraffin-embedded tissue into sterile Eppendorf tubes; for each neoplastic component, sections were used in which one of tumor population was largely predominant, with only negligible intermingling with the other cell populations. Microscopically uninvolved skin served as normal background control. DNA specimens were assessed by means of a custom-designed panel targeting: all exons of *HRAS*, *KRAS*, *GNAQ*, *GNA11*, *GNAS*, *KIT*, *RET*, *NF1*, *PDGFRA*, *TP53*, *IDH1*, *IDH2*, *H3F3A*, and *H3F3B*; targeted regions of *NRAS*, *BRAF*, *CTNNB1*, *MAP2K1*, and *PTEN*; and the promoter region of *TERT*. Variant analysis and interpretation of next generation sequencing data were performed using the catalogue of somatic mutations in cancer (COSMIC). NGS analysis revealed identical, likely pathogenic mutations in the oncosuppressor *TP53* (c.635_636delTT p.Phe212fs; frameshift mutation) and *NF1* (c.5494 G > T p.Glu1832Ter; nonsense mutation); such mutations were separately detected in both the conventional DM and the pseudoglandular component. Additionally, both tumor cell populations exhibited an identical mutations of unknown pathogenic significance in *RET* (c.184 G > A p.Glu62Lys), further supporting a close genetic relationship of the pseudoglandular component with the rest of the neoplasm.

Computed tomography scan of the scalp showed extension of the neoplasm down to the underlying periosteum. No evidence of locoregional metastatic spread was observed on radiological imaging. A wide excision with clean lateral and deep margins was performed. At 12-month follow-up, the patient is asymptomatic with no evidence of a recurrence.

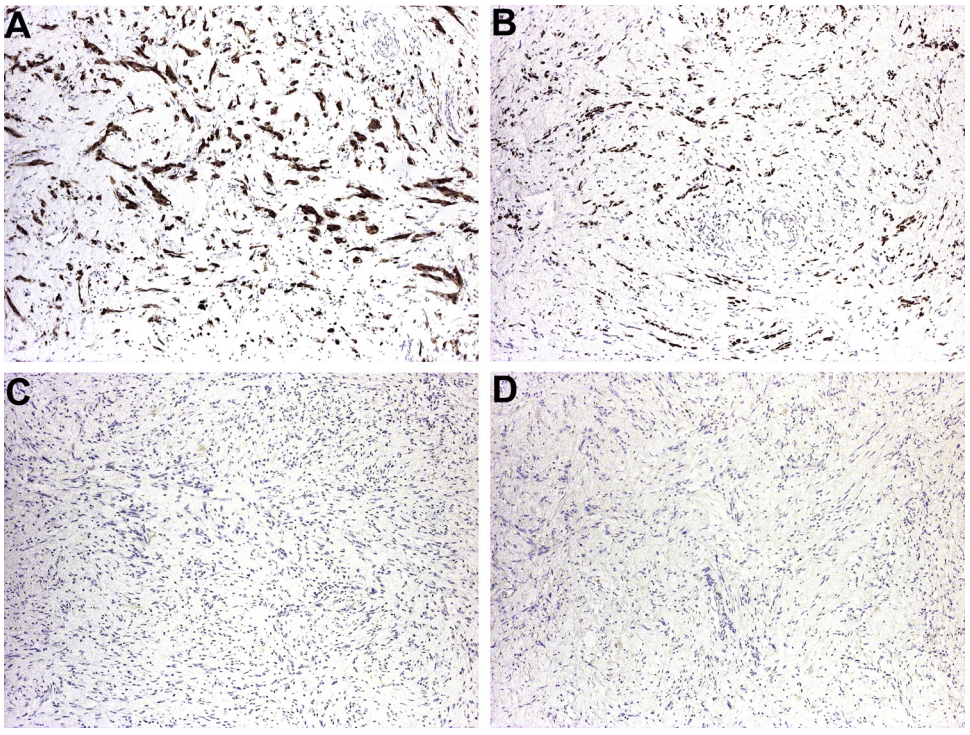

Fig. 2. Immunohistochemical staining of the desmoplastic spindle-cell population, showing strong and diffuse positivity for S-100 (**A**; original magnification 10×) and SOX-10 (**B**; original magnification 10×), in contrast to complete lack of expression of Melan-A (**C**; original magnification 10×) and pan-citokeratin AE1/AE3 (**D**; original magnification 10x).

3. Discussion

DM is a rare subtype of spindle cell MM which accounts for less than 5% of all MM cases [1,2]. The histologic hallmark of DM is the presence of a predominantly dermal proliferation of spindled/fibroblast-like cells within a desmoplastic stroma; by definition, the collagen content of the latter must be greater than 90% of the whole neoplastic mass [1–3]. We described an unusual case of deep DM arising from the dense layer of scalp connective tissue (*i.e.*, the superficial fascia), and characterized by extensive, pan-cytokeratin-positive pseudoglandular differentiation. According to current nomenclature, our case should be classified as mixed DM, as the epithelioid, non-desmoplastic, carcinoma-like cell population constituted more than 10% of the entire neoplasm [13]. NGS data was consistent with the final diagnosis of DM, additionally supporting a close genetic relationship between the conventional tumor part and the pseudoglandular component.

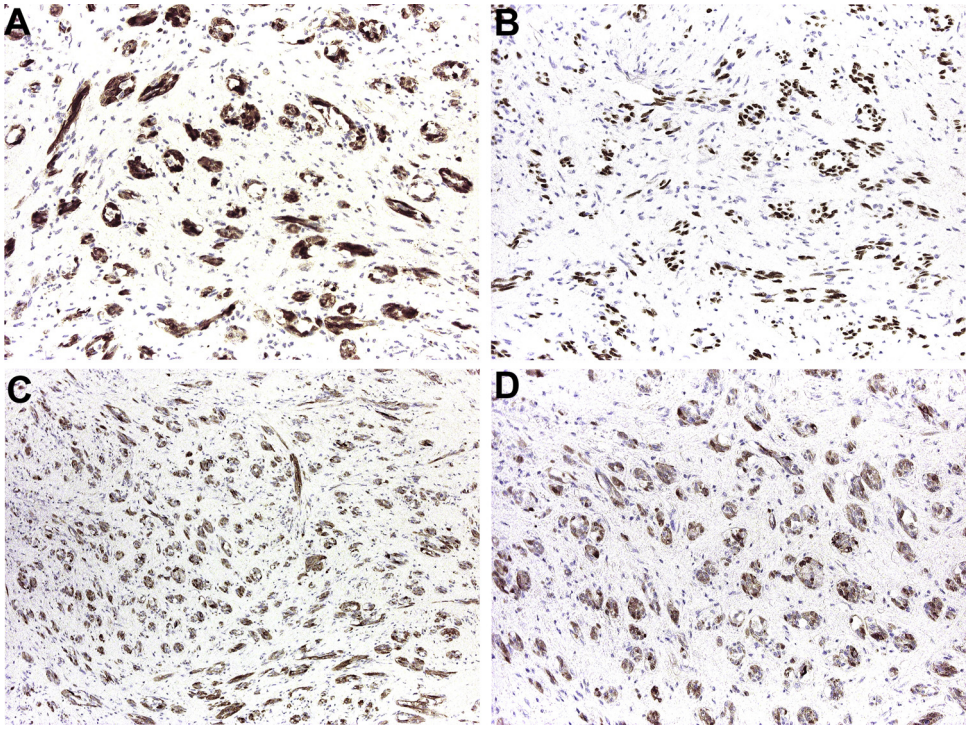

Fig. 3. In the pseudoglandular cell population, widespread expression of S-100 (**A**; original magnification 20×) and SOX-10 (**B**; original magnification 20×) is mirrored by diffuse positivity for pan-citokeratin AE1/AE3 (**C**, **D**; original magnification 10×, 20×).

Recent genetic studies of DM have confirmed its uniqueness [4,14,15]. DM is normally characterized by an extraordinarily high median mutation burden, with a striking prevalence of C > T transitions at dipyrimidine sites, thus implicating a dominant mutagenic role for UV-radiation [4,15]; only exceptional cases of DM have been reported to arise on sun-protected skin sites and exhibit a markedly lower overall mutation rate [4]. Conventional MM oncogenic mutations in *BRAF*, *NRAS*, *GNAQ/GNA11*, and *KIT* are usually absent in DM [4,15,16]; conversely, a unique set of oncogenes and oncosuppressor genes appears to be specifically involved in the pathogenesis of DM, including *NF1* (52–93%) and *TP53* (40–60%) [4,14,15]. *NF1* inactivation likely plays a role in the MAP-kinase pathway hyperactivation [17,18], while the majority of observed *TP53* genetic events are missense mutations at the level of the DNA binding domain, leading to functional inactivation of the corresponding oncosuppressor protein [4,15,19]. NGS assessment in our case revealed the distinct presence of pathogenic, inactivating mutations in *NF1* and *TP53* throughout the two neoplastic populations, thus supporting the final diagnosis of an atypical, deep variant of DM.

Our case exhibited several clinico-pathological features in keeping with conventional DM, including clinical presentation (a slow-growing, large tumor arising on chronically sun-damaged skin), histological evidence of an accompanying patchy lymphoid infiltrate, and IHC loss of melanocytic differentiation markers (Melan-A and HMB-45) [1–3,20,21]. Lack of a junctional, *in situ* component may be observed in up to 50% of DM cases [2,3]. Our case, however, was unusual because the neoplasm originated from the superficial fascia of the scalp, with sparing of the overlying subcutaneous fat and dermis, as demonstrated upon extensive sampling of excisional tissue. Such histological presentation is unprecedented, as in reported cases of DM the involvement of hypodermis and deeper tissues always occurred due to downward extension from the overlying dermis [1–3]. We speculate that in our case the pathogenic mutations in *NF1* and *TP53* might have occurred in a deep-seated neural crest-derived precursor cell, with no significant role played by chronic sun damage, leading to the unusual development of an intrafascial DM.

The detection of the same oncogenic mutations in *TP53* and *NF1*, as well as of a likely passenger *RET* mutation in both the conventional DM population and the pseudoglandular component supported the final diagnosis of DM with pseudoglandular differentiation. Heterologous neural differentiation is commonly observed in DM in the form of schwannian/perineurial features as well as neurotropism [22]; osteoclast-like giant cell differentiation was exceptionally reported as well [23]. Coexistence of desmoplastic and pseudoglandular patterns in MM has been described in a single case of primary cutaneous signet-ring cell MM [8]; nevertheless, to the best of our knowledge the occurrence of extensive pseudoglandular differentiation in primary DM has never been reported in the available literature. Pseudoglandular MM is characterized by extensive discohesion within cords and nests of malignant cells, resulting in formation of adenocarcinoma-like pseudolumina [5,6,8,9]. Central pseudolumina may develop through several mechanisms, including diffuse loss of intercellular junctions within melanocytic nests, central necrosis of neoplastic nodules, and/or widespread vacuolization of melanocytes cytoplasm [8,9].

Phenotypic plasticity in MM may be observed in the form of variable loss of melanocytic antigens as well as abnormal expression of heterologous lineage markers [24,25]. Aberrant expression of non-vimentin intermediate filaments, including cytokeratins, has been shown to be a relatively frequent occurrence in MM [11]. Incidence of aberrant cytokeratin expression seems to be similar between primary and metastatic MM, while exhibiting a predilection for malignant melanocytes with an epithelioid morphology [11,26,27]. Interestingly, gland-like structures in reported cases of pseudoglandular MM did not show any loss of conventional melanocytic antigens and/or aberrant expression of epithelial markers [8,9]; accordingly, pseudoglandular differentiation in MM has been regarded as a morphological artefact rather than as the result of lineage reprogramming [5,6,8]. On the contrary, reversal of melanocytic phenotype, with negativity for S-100 and SOX-10 paralleled by aberrant expression of cytokeratins and EMA, has been reported in exceptional cases of metastatic melanoma with true adenocarcinomatous transdifferentiation [28]. The gland-like structures observed in our case failed to express glandular cytokeratins such as CK-7 and CK-20, while retaining expression of S-100 and SOX-10; additionally, no EMA staining was observed at the level of the luminal surface. Accordingly, we believe that the morphological features observed in this report should be regarded as pseudoglandular changes rather than true glandular transdifferentiation.

The differential diagnosis of a deep-seated tumor characterized by epithelioid nests growing within a desmoplastic stroma, in addition to aberrant expression of cytokeratins, is wide and challenging. Biphasic synovial sarcoma (SS) is characterized by the intermingled combination of an epithelial and a spindled malignant cell population [29,30]. Pan-cytokeratin-positive glandular elements are common in the SS epithelial population, while stromal hyalinization may be seen in the spindle-cell component [31,32]. Significant expression of CK-7 and EMA, however, is usually observed in SS; furthermore, while at least focal expression of S-100 and SOX-10 may be seen in a minority of SS cases, lack of IHC nuclear staining for TLE1 virtually rules out a diagnosis of SS [29,31,32]. The combination of nests and cords of epithelioid cells proliferating within a highly hyalinized stroma is also typical of sclerosing epithelioid fibrosarcoma (SEF), a fibrosarcoma variant characterized by distinctive fusions transcripts involving EWSR1 or FUS and CREB3L-1/-2 [33]. While focal reactivity for pan-cytokeratins and/or S-100 may be occasionally seen in SEF, the combination of diffuse SOX-10 expression and negativity for MUC-4 is inconsistent with SEF [33,34].

Rare cases of MPNST may feature a glandular component intermingled with the fascicles of malignant spindle cells [35]. The glandular structures in MPNST may be benign- or malignant-looking; IHC positivity for pan-cytokeratins is usually accompanied by expression of EMA, CK7 and/or CK20, as well as CEA, while expression of S-100 and SOX-10 appears to be lost in the glandular component [35]. Additionally, diffuse, widespread expression of S-100 and SOX-10 in the spindle-cell population would be unusual in MPNST, with preserved nuclear expression of H3K27me3 further militating against such diagnosis [36]. Myoepithelial carcinoma (malignant myoepithelioma) may show a combination of spindled and epithelioid cells arranged in small nests and cords with gland-like features, but a multilobulated growth pattern is more typically observed, harboring at least focal chondromyxoid areas [37]. Additionally, myoepithelial carcinoma is usually characterized by IHC positivity for EMA as well as for other myoepithelial markers, including alpha-SMA, GFAP, calponin, and/or p63 [37]. Lastly, diffuse expression of S-100, SOX-10, and INI-1, coupled with negativity for EMA, alpha-SMA, desmin, as well as lineage-specific nuclear transcription factors such as p63, ERG, and MyoD1, allows to rule out additional diagnoses such as metastatic carcinoma, carcinosarcoma, epithelioid sarcoma, epithelioid angiosarcoma, epithelioid leiomyosarcoma, and spindle cell/sclerosing rhabdomyosarcoma [29–31].

In conclusion, we described a peculiar case of a primary intrafascial DM with pseudoglandular differentiation. Prior to this report, pseudoglandular features had never been described in DM. Additionally, our case is highly unusual because of the deep origin of the tumor, arising below the subcutaneous fat of the scalp, and the aberrant expression of cytokeratins in the pseudoglandular component, thus posing a challenging differential diagnosis with several soft tissue tumors.

Declarations of founding sources

None.

Declaration of Competing Interest

None.

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