CASE REPORT

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Malignant cutaneous mixed tumor with sebaceous differentiation

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Abstract

Malignant cutaneous mixed tumor (CMT) is a very rare adnexal tumor with biphasic differentiation. In rare cases, a benign CMT (chondroid syringoma) undergoes malignant transformation. Sebaceous differentiation in a cutaneous malignant mixed tumor has not been previously reported. We present a malignant CMT with sebaceous differentiation, which occurred on the scalp of an 81-year-old man. The tumor showed epithelial elements composed of relatively small and bland-appearing ductal and cord-like structures lined by small, cuboidal-shaped adnexal cells, with a few large, dilated gland-like spaces lined by larger, apocrine-appearing cells with abundant eosinophilic-staining cytoplasm. However, the majority of the epithelial component was composed of nests and islands of markedly enlarged and atypical cells with pale/clear to ground-glass cytoplasm. Focally, there was sebaceous differentiation identified, in the form of prominent multivacuolated cytoplasm, with nuclear indentations. The stroma showed a mixture of myxoid and hyalinized/chondroid-appearing areas with focal calcifications. There was strong and diffuse staining of the sebaceous cells by cytokeratin (CK) 7, epithelial membrane antigen (EMA), and androgen receptor (AR). Mismatch repair proteins were investigated by immunohistochemistry, without evidence of loss of expression of MutS protein homolog 6 (MSH6), MutS protein homolog 2 (MSH2), MutL protein homolog 1 (MLH1), or postmeiotic segregation increased 2 (PMS2) in the sebaceous cells.

Keywords: sebaceous carcinoma, cutaneous mixed tumor, chondroid syringoma, malignant mixed tumor, Muir–Torre syndrome.

Introduction

Malignant cutaneous mixed tumor (CMT) is a very rare entity. There are essentially four scenarios in which malignancy can be found in a CMT: in the first situation, the malignant changes are present *de novo* (*i.e.*, when the tumor is first diagnosed) [1, 2]. The second possibility is a benign CMT, which has often been present for many years, undergoes malignant transformation and rapid growth [3, 4]. In the third scenario, a malignant mixed tumor from another organ (such as the salivary glands) secondarily infiltrates the overlying skin [5, 6]. In the final situation, a malignant mixed tumor can very rarely develop in a pre-existent apocrine or eccrine adnexal non-mixed tumor, such as a spiradenoma [7].

In each of these four scenarios, malignancy can be seen either in the epithelial [8, 9] and/or (more rarely) in the mesenchymal component [10]. Additionally, atypical morphological features in the epithelial component of cutaneous mixed tumors have been reported in some cases, but have an uncertain clinical meaning, and the term "atypical" mixed tumor of the skin has been coined to describe such cases [11].

Although previously reported in some salivary gland mixed tumors, sebaceous differentiation in a primary cutaneous malignant mixed tumor has not been described to date. Therefore, this represents a very rare and unusual phenomenon, but emphasizes the morphological diversity and multiple lines of differentiation, which can be seen in CMTs.

Case presentation

An 81-year-old man presented to the Dermatology Clinic complaining of a nodular lesion on his scalp. Clinical examination showed a subcutaneous, mobile 1.2 cm nodule, which was apparently cystic, on the mid frontal scalp (above the hairline), from which a biopsy was taken. Given the diagnosis of malignancy, and the involvement of the edges of the biopsy, a wide excision was subsequently performed, with only minimal residual tumor and clear margins in the excisional specimen.

Histological sections showed a tumor involving the dermis and the subcutaneous tissue, composed of both epithelial and mesenchymal/stromal elements (Figure 1A). The tumor showed an irregular growth pattern, focally infiltrating into the fat (Figure 1B). In the central areas of the tumor, the epithelial structures consisted of a population of relatively small and bland-appearing ductal and cord-like structures lined by small, cuboidal-shaped adnexal cells (Figure 2A), with a few large, dilated, gland-like spaces lined by larger apocrine-appearing cells (Figure 2B) with abundant eosinophilic-staining cytoplasm. However, the majority of the epithelial component was composed of nests and islands (Figure 3A) of markedly enlarged and atypical cells with abundant pale to clear

to "ground-glass" cytoplasm (Figure 3, B and C). In some areas, definitive evidence of sebaceous differentiation was seen in the form of large multi-vacuolated cells with clear cytoplasm and nuclear indentations (Figure 4, A–C). Foci of sebaceous differentiation were also seen in the infiltrative-appearing areas (Figure 4D). The stroma showed a mixture of myxoid and hyalinized/chondroid-appearing areas with focal calcifications. Some apparent foci of necrosis were also identified (Figure 3D).

Immunohistochemical study was performed for the following antibodies: cytokeratin (CK) 5/6 (Dako, clone D5/16 B4), CK 7 (Dako, clone OV-TL 12/30), S100 protein (Dako, Autostainer Link48), p63 (Dako, clone DAK-p63), epithelial membrane antigen (EMA) (Dako, clone E29) and androgen receptor (AR). The deparaffinization plus antigen retrieval was automatically performed in the PTLink from Dako, at a low pH. The immunostaining was automatically performed in the Autostainer Link 48 from Dako. The slides were revealed with 3,3'-Diaminobenzidine and counterstained with Hematoxylin.

In spite of the irregular tumoral boundaries, immunohistochemical studies showed that CK 5/6, S100, and p63 strongly stained an apparently diffuse myoepithelial layer surrounding most of the tumor cords and nests, providing no definite evidence of invasion. EMA and AR stainings strongly highlighted the cytoplasm of many of the large, atypical cells, including the areas with sebaceous differentiation (Figure 5). CK 7 staining was also strongly and diffusely positive, both in the central and peripheral parts of the tumor.

Given the presence of sebaceous differentiation in this tumor, mismatch repair (MMR) proteins were investigated by immunohistochemistry, without evidence of loss of expression of MutS protein homolog 6 (MSH6) (Dako, clone EP49), MutS protein homolog 2 (MSH2) (Dako, clone FE11), MutL protein homolog 1 (MLH1) (Dako, clone ES05) or postmeiotic segregation increased 2 (PMS2) (Dako, clone EP51) in the tumor. Following the current advice in the literature [12], no additional studies were performed to rule out Muir–Torre syndrome, but a note was made advising that the patient should be referred to medical genetics in case of strong clinical suspicion of Muir–Torre syndrome.

A diagnosis of primary cutaneous malignant mixed tumor with sebaceous differentiation (favoring sebaceous carcinoma, at least *in situ*, arising in a mixed tumor) was rendered. Although definitive evidence of invasion was not identified, given the focally infiltrative-appearing areas, a note remarking that focal invasion could not be excluded was included in the report. A computed tomography (CT) scan of the neck was negative for adenopathy, and no adjuvant therapy was recommended after complete excision with clear margins.

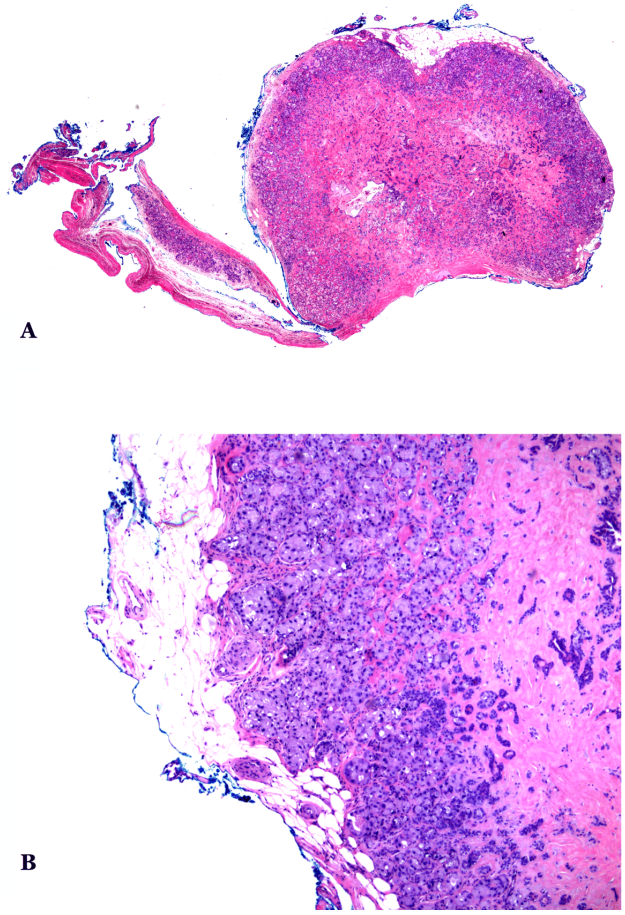

Figure 1 – ***(A) Low power view of the tumor involving the dermis and the subcutaneous tissue, composed of both epithelial and mesenchymal/stromal elements; (B) The tumor showed an irregular growth pattern, focally infiltrating into the fat. HE staining: ×40 (A); ×100 (B).***

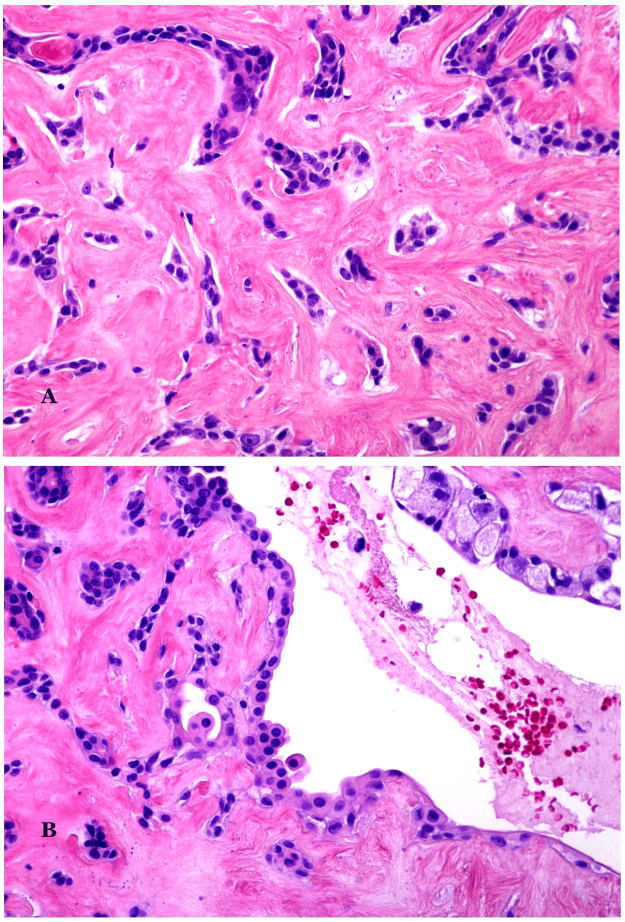

Figure 2 – ***Central areas of the tumor: relatively small and bland-appearing ductal and cord-like structures lined by small, cuboidal-shaped adnexal cells (A), with a few large, dilated, gland-like spaces lined by larger apocrine-appearing cells (B). HE staining: ×200 (A and B).***

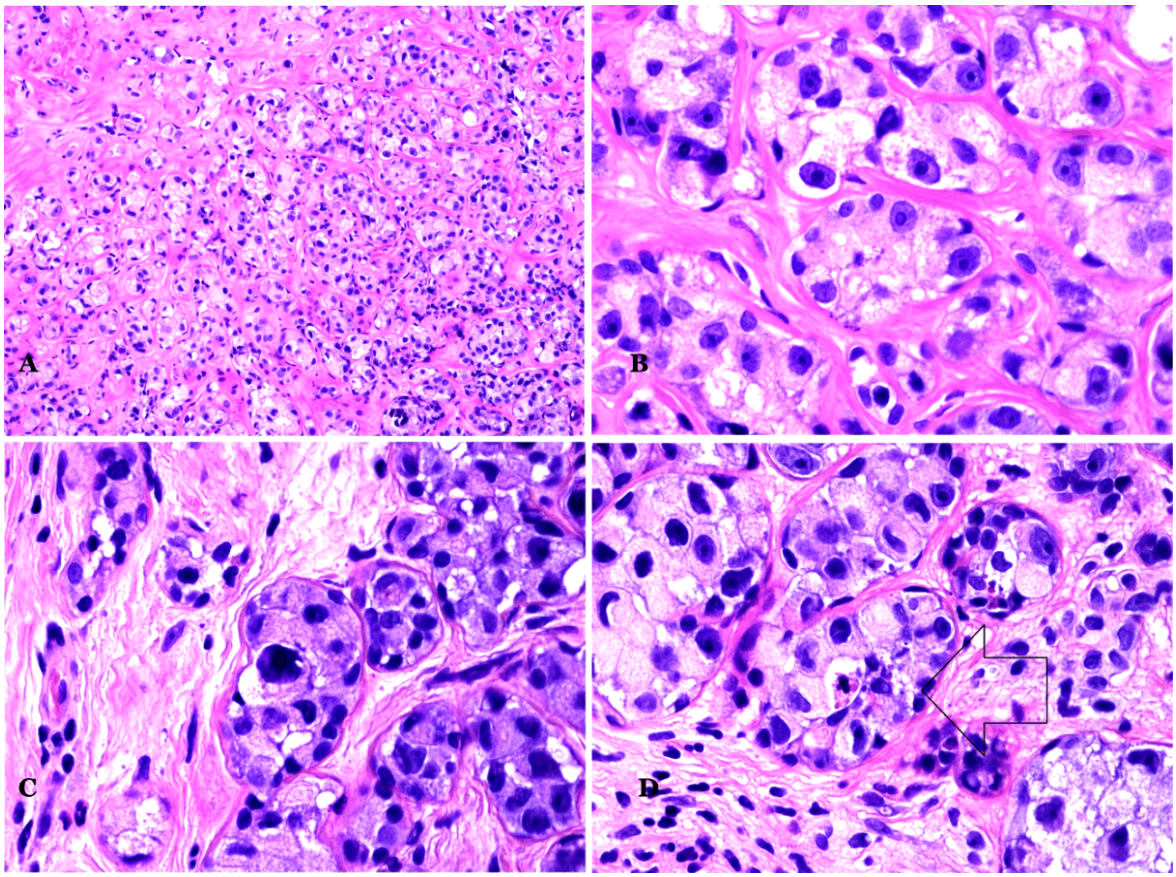

Figure 3 – ***The majority of the epithelial component was composed of nests and islands (A) of markedly enlarged and atypical cells with abundant pale to clear to ground-glass cytoplasm (B and C). Some foci of necrosis were also identified (D) (Arrow). HE staining: ×100 (A); ×400 (B–D).***

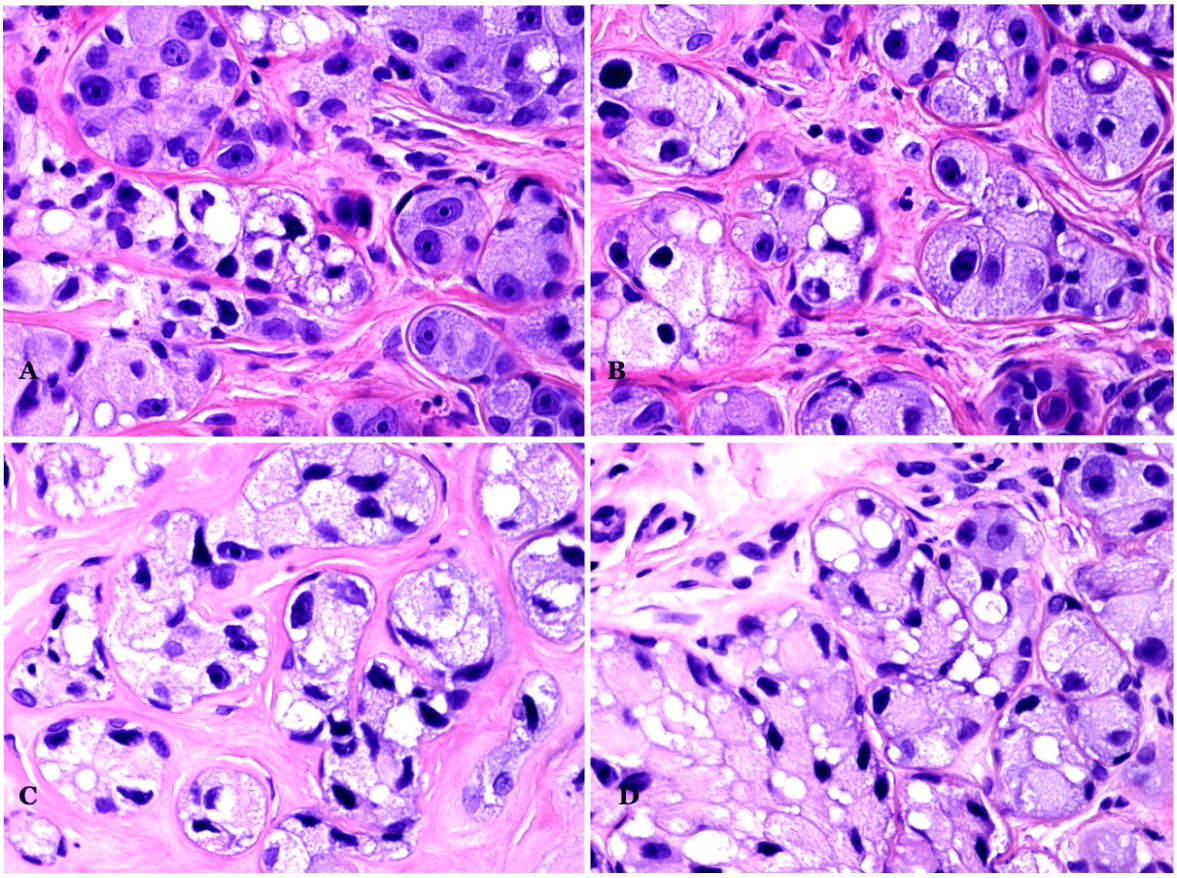

Figure 4 – ***Sebaceous differentiation was seen in the form of large multivacuolated cells with clear cytoplasm and nuclear indentations (A–C), even in the infiltrative-appearing areas (D). HE staining: ×400 (A–D).***

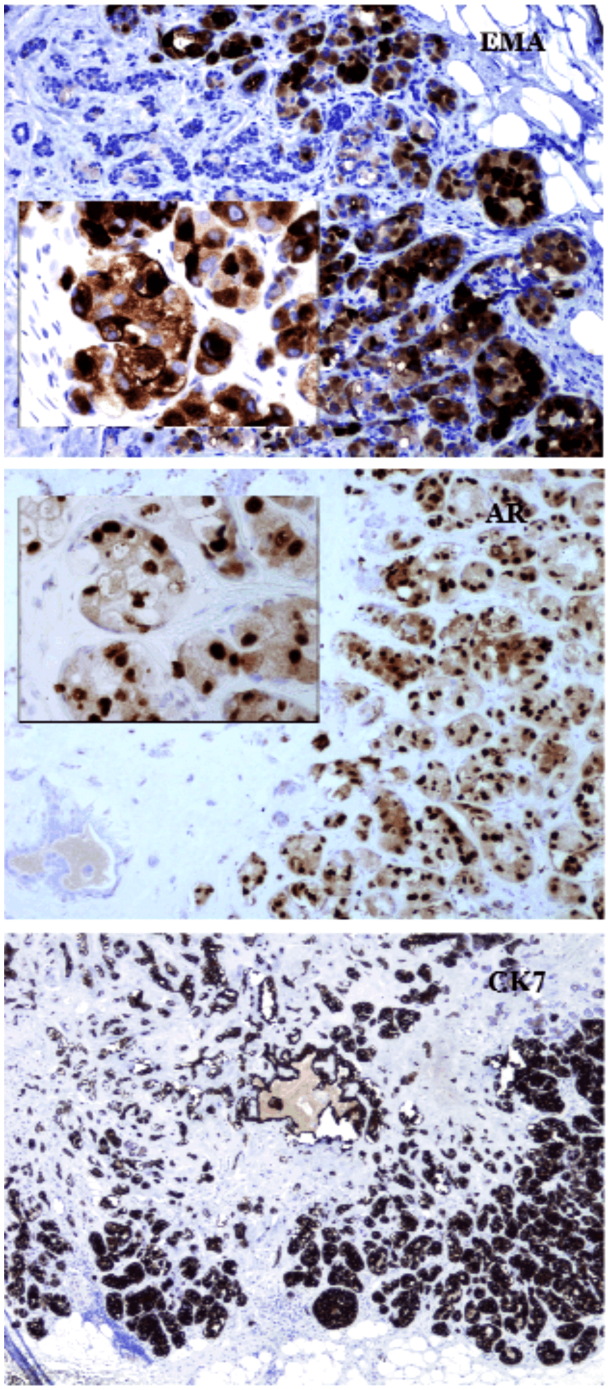

Figure 5 – ***Immunoexpresion of epithelial membrane antigen (EMA) (top – ×100; inset, ×400) and androgen receptor (AR) (middle – ×100; inset, ×400) by many of the large, atypical cells, including the areas with sebaceous differentiation. The tumor was positive for CK 7 (bottom – ×100).***

Discussion

Sebaceous carcinoma arising in a benign mixed tumor (pleomorphic adenoma) is a very rare entity, with only very few cases published in the literature, mainly involving the parotid or lacrimal glands [13–15] as well as exceptional cases reported in the veterinarian pathology literature [16]. In addition, areas of benign sebaceous differentiation have been described in mixed tumors of the palate [17] or the skin [18, 19]. In the latter organ, sebaceous changes occur mainly in tumors located on sites in which sebaceous glands are prominent, such as the face or the ears [20]. Kazakov *et al.* reviewed 244 cases of cutaneous apocrine mixed tumors, emphasizing the spectrum of differentiation and metaplastic changes that occur in the epithelial, myoepithelial, and stromal components [21]. They found sebaceous differentiation in 28 (11%) cases, but only as benign elements, such as mature sebocytes or sebaceous ducts [21].

Requena *et al.* found sebaceous differentiation in five out of eight (62.5%) benign CMTs [18]. Wong *et al.* reviewed eight cases of benign cutaneous adnexal tumors, and found sebaceous structures in five (62.5%) cases as lobular arrangements or solitary sebaceous cells [19]. Hassab-El-Naby *et al.* also found sebaceous differentiation in "a few neoplasms" [22]. Sebaceous changes should not be confused with physaliphora-like cells or clear cells, which are often found in eccrine mixed tumors [23]. These benign sebaceous changes described so far in the literature in cutaneous mixed tumors have an immunoprofile that is similar to normal sebaceous glands, with expression of CKs 1, 5, 10, 14, 6, 7, and 14 [20]. In addition, EMA has been found in areas with sebaceous differentiation [19].

Therefore, no cases of malignant cutaneous tumor with sebaceous differentiation or sebaceous carcinoma ex cutaneous mixed tumor have been reported to date, and our case represents a very rare and unusual finding. Although Kazakov *et al.* had reported some "atypical" cutaneous mixed tumors that we commented on above, none of these cases showed sebaceous differentiation [11].

Regarding the histogenesis of sebaceous differentiation in mixed tumors, some authors have suggested that at least the cases found in the salivary glands might represent an aggressive form of mucoepidermoid carcinoma [13]. Cutaneous derived sebaceous tissue displaced into the salivary gland during embryogenesis has also been mentioned as a probable pathogenic mechanism by some authors [24]. In cutaneous cases, such a displacement would obviously not be necessary, since folliculosebaceous units are a normal component of the skin. Nevertheless, it is interesting to mention that cases of cutaneous mixed tumors connecting to a hair follicle *via* an apocrine duct have been described [25]. In fact, it was Hassab-El-Naby *et al.* who first suggested that apocrine cutaneous mixed tumors show differentiation towards the folliculosebaceous apocrine unit [22]. Lastly, the evolution of the sebaceous component from an undifferentiated intercalated or striated ductal progenitor cell with the capacity to differentiate into sebaceous, ductal, or squamous components has also been suggested [26, 27]. Such a mechanism is at least plausible for the sebaceous tumoral component in salivary gland mixed tumors, since some otherwise normal salivary glands may show benign sebaceous structures [28, 29].

In our case, given the unusual sebaceous differentiation, we investigated the immunohistochemical status of the MMR proteins (MSH-2, MSH-6, MLH-1, and PMS-2), and found preserved expression of all four markers. There are no current guidelines or consensus on the necessity of performing these studies in cases of mixed tumors with sebaceous differentiation. However, determining the MMR protein status has been recommended in cases of

basal cell carcinoma with sebaceous differentiation [12], which is a context not so different from the current one. Given the preservation of the MMR status, we did not pursue additional studies, following the current opinion on the management of patients with cutaneous sebaceous neoplasias [12]. However, since MMR mutations are responsible for only half of hereditary non-polypoid colorectal cancer syndromes identified by pedigree criteria only, and since some familial colorectal cancers do not show high grade microsatellites instability, some recommend carrying on with the clinical investigations if there is a strong clinical suspicion, such as the fulfillment of the Amsterdam criteria [30].

Our case was found on the scalp. Although benign CMT typically occur in the head and neck region, this is not the most common situation in malignant mixed tumors, which are primarily located on the trunk and extremities [31, 32]. However, occasional cases of malignant cutaneous chondroid syringoma have been described on the face [33] and the scalp [8].

Conclusions

We report the first case of a very rare malignant cutaneous mixed tumor with sebaceous differentiation, likely representing sebaceous carcinoma *in situ* arising in a benign mixed tumor. This finding emphasizes the broad morphological diversity of benign and malignant cutaneous, and the likely derivation of these tumors from the folliculosebaceous apocrine unit. In addition, we also investigated the MMR status of this case, finding no loss of expression of these markers.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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