Cutaneous mixed tumor with lipomatous stroma

**Aim:** Mixed tumors are usually composed of two components, one epithelial and the other mesenchymal. The latter component is commonly myxoid or myxochondroid; a massively lipomatous stroma is very unusual. To date, only two cases of mixed tumor of the skin have been reported with this type of stroma.

**Methods and results:** We report the case of a 61-year-old man with a mixed tumor situated on the hand, an unusual site for these tumors, with over 90% of the tumor composed of adipose tissue. The tumor was a well-circumscribed, 4.5-cm mass, with the gross appearance of a lipoma. The lipomatous stroma contained nests and ribbons of epithelial cells, with occasional tubular structures, surrounded by a scarce amount of fibromyxoid tissue. Immunohistochemical study showed findings similar to those seen in classic mixed tumors.

**Conclusion:** Together with a few other cases in the skin and parotid gland, this report shows how massive adipose differentiation can arise in a mixed tumor of the skin.

showed a soft mass with a smooth, slightly undulated, yellow surface. The cut surface was of a homogenous yellow color with a few small scattered brownish nodules (Fig. 1).

Histopathological study showed a mass, more than 90% of which was composed of adipose tissue. Externally, the mass was well circumscribed by a thin connective capsule. Eccrine gland remnants were visible in the peritumoral subcutaneous tissue. Scattered within the stromal adipose tissue were nests and cords of epithelial cells, which were often branched and compressed by the adipose tissue, adopting a septal pattern (Fig. 2). The cells within the nests lacked any order, showed poor cohesiveness, with intercellular separations and even some small cavities. They occasionally formed a whirlpool pattern around a small lumen. Some epithelial cords contained well-conformed glandular lumina, occasionally with just a double layer of cells and flattening of the internal layer. A PAS-positive basal membrane was frequently evident around the epithelial structures. The nuclei of the epithelial cells were ovoid or fusiform, with scarce pleomorphism, homogenously distributed chromatin, and small nucleoli, although among which were occasional large, moderately pleomorphic nuclei, with prominent nucleoli. No mitotic figures were observed.

Around the epithelial nests was a discrete amount of myxoid stroma, with Alcian blue-positive mucin and epithelioid, plasmacytoid, or fusiform myoepithelial cells, interspersed with adipocytes. A few cells in this myxoid stroma had clear variable-sized cytoplasmic vacuoles, establishing histological continuity between the epithelial component, the cellular myxoid, and the adipose tissue. A marked border of small vessels was situated in apposition to the epithelial nests. The lipomatous stroma was composed of variable-sized mature adipocytes, with occasional dilated venous vessels. No chondroid or other sort of differentiation was visible, nor were there any lipoblasts.

The immunohistochemical study of the epithelial cells was positive for the high- and low-weight cytokeratins (AE1–3), CAM5.2, and cytokeratin 7. Cytokeratin 20 was negative. Staining with EMA was focal and confined mainly to the luminal surface of the ductal structures. CEA occasionally stained groups of cells forming ductal lumina, and GCDFP-15 stained cells with a granular eosinophilic cytoplasm present in some epithelial nests. S-100 frequently stained the epithelial cells in the nests, although irregularly, while the cords and the cells forming tubules were negative. Vimentin was positive in some epithelial cells, generally in the periphery of the nests, and actin showed a moderate or weak intensity in some epithelial nests. Bcl-2 staining was weak, with occasional strong positivity in some cell groups. P53 was negative, and the proliferative activity detected by Ki67 was very low and relegated to the larger cell nests. The cells in the myxoid stroma beside the nests, including the vacuolated cells, were often positive for vimentin, AE1–3, and CAM5, and also for S-100 (Fig. 2). Actin was only weakly positive in a few cells. Mature adipocytes were positive for S-100 and, in the areas near cell nests, some small adipocytes, in transition from myoepithelial vacuolated cells to mature adipocytes, also stained for cytokeratins.
Discussion
This tumor represents an exceptional form of mixed tumor whose mesenchymal component was composed almost exclusively of adipose tissue. As far as we are aware, only five other similar cases have been reported. The first, by Ng and Ma, concerned the submandibular gland. Later, two tumors were reported in the parotid gland and another two in the subcutaneous tissue of the head. Histologically, the tumors were mostly similar; they were well circumscribed, with a massive adipose stroma occupying over 90% of the tumor, epithelial cords with a septal-like pattern, as though they had been compressed by the growth of the adipose tissue, and the formation of glandular ducts or lumina within the epithelial structures. Surrounding these structures was a variable amount of myxoid stroma with dispersed myoepithelial cells, some of which contained prominent cytoplasmic vacuoles, which have been interpreted as representing a transition between these cells and mature adipocytes. No chondroid or other type of tissue was present, and no lipoblasts were seen.

Two of the mixed lipomatous tumors reported previously presented some differences in their histological features. The tumor in the submaxillary gland, reported by Ng and Ma, was mainly composed of fusiform cells in a myxoid background, with many of the cells containing prominent vacuolated cytoplasmic vacuoles, which have been interpreted as representing a transition between these cells and mature adipocytes. No chondroid or other type of tissue was present, and no lipoblasts were seen.

The two lipomatous mixed tumors of the skin, situated in the glabellar and the high occipital regions, respectively, were related to chondroid syringoma/mixed tumor of the skin and considered a variant of these. Our case, however, was situated on the palm of the hand, a very unusual site for this type of tumor. Nevertheless, the tumor was clearly histologically similar to the above cases, and the pattern of immunohistochemical reactivity was similar to that of the chondroid syringomas, including positivity, although focally, for CEA and GCDFP-15. Moreover, in the scarce subcutaneous tissue adjacent to the tumor were a few tubules of normal eccrine gland.

It has recently been accepted that mixed tumors and myoepitheliomas can also occur in soft tissue, with histopathological and immunohistochemical features similar to those of the salivary gland or the skin. Most of these tumors are on the limbs; approximately 20% show ductal differentiation and over half primarily affect the subcutaneous tissue, as did our tumor and the other two lipomatous mixed tumors of the skin. Some of these tumors may arise in eccrine glands in the subcutaneous tissue but, as discussed by Kilpatrick et al., notable differences exist between the chondroid syringoma and the mixed tumor of soft tissues, not only in their histological characteristics, dominated by myoepithelial differentiation, but also in the location, mainly on the limbs, and in their biological behaviour with recurrences and even metastasis.

The source of the adipocytes in mixed tumors has been studied. While the presence of focal groups of mature adipocytes is generally attributed to entrapment within the adipose tissue by the growing tumor, this hypothesis lacks sense in lipomatous mixed tumors because the adipose tissue is the main component of the tumor, surrounding epithelial cords and nests, and circumscribed by a fine connective capsule as in lipomas. Thus, in our tumor and those described previously, the adipose tissue is a form of mesenchymal differentiation which may very occasionally arise in mixed tumors.

Recent molecular and genetic studies have provided evidence of a clonal origin for salivary gland mixed tumors, with a common progenitor cell, probably epithelial, which would give rise to mesenchymal cells via a process of transdifferentiation. This hypothesis was also supported by Miocac et al. for their lipomatous mixed tumor of the skin, based on the histopathological, ultrastructural, and immunohistochemical findings. Histologically, in their case as well as in ours, a clear transition was evident between the epithelial and myoepithelial cells and the mature adipocytes, with the presence of vacuolated fusiform cells beside the epithelial nests, which Miracco et al. called intermediate cells. The immunohistochemical study was also in agreement with the idea of transdifferentiation, as S-100 positivity could be seen in the epithelial cells, the myoepithelial cells, and the adipocytes, while the vacuolated fusiform cells and some small adipocytes near the epithelial nests were positive for cytokeratins (AE1–3). Interestingly, however, the adipose differentiation seems to exclude another type of mesenchymal differentiation, the common chondroid differentiation, because no chondroid tissue has been detected in any of the lipomatous mixed tumors so far reported.
Grossly, the lipomatous mixed tumor is easily confused with superficial subcutaneous lipomas, which lack epithelial elements, and the more unusual adenolipomas of the skin described by Hitchcock et al. This latter neoplasm also contains a few eccrine gland structures within a lipomatous stroma, but only focally and near the dermis, resembling entrapped structures rather than a neoplastic component.

In conclusion, we describe a case of a mixed tumor with a lipomatous stroma, probably related to the chondroid syringoma, but situated on the hand, which is uncommon for these tumors. This type of tumor highlights the ability for massive adipose differentiation, which may occasionally arise in mixed tumors.

References