Lipomatous Mixed Tumor of the Skin
Hung-Wei Lin Han-Nan Liu

Background: Mixed tumors of the skin showing extensive lipomatous change have been reported scantily in the literature. The cause of this change is under debate and have generally been attributed to metaplasia of the tumor cells or less commonly, lipomatous degeneration.

Objective: This study was aimed to evaluate how often the lipomatous change happen in mixed tumors and attempt to elucidate the etiology of such changes via histopathological and immunohistochemical methods.

Methods: Cases diagnosed as cutaneous mixed tumors within the past twenty years were retrieved from our archives and reevaluated. Those with extensive lipomatous component were submitted to special staining: smooth muscle actin, glial fibrillary acidic protein, and S-100 protein

Results: Twenty-nine cases were reviewed histopathologically. Varying degrees of lipomatous differentiation was noted in thirteen (45%) cases. In four (14%) of them, the lipomatous component constituted larger than 20% of the total stromal component. The lipomatous cells strongly expressed S-100 protein, but reacted negatively to smooth muscle actin or glial fibrillary acidic protein. Some intermediate cells were noted in intermediate zones.

Conclusion: Lipomatous change in mixed tumors of the skin may be more common than previously thought. The strong expression of S-100 protein in the lipomatous cells and the finding of intermediate cells support the notion that metaplasia of myoepithelial cells plays a role in the stromal differentiation of mixed tumors. (Dermatol Sinica 27: 85-92, 2009)

Key words: Mixed tumor, Chondroid syringoma, Lipomatous, Metaplasia, Myoepithelial

INTRODUCTION
Mixed tumors are benign neoplasms that are referred to as pleomorphic adenomas and chondroid syringomas according to the site of origin, that is, the parotid gland and the skin, respectively. Chondroid syringomas are rare tumors that present as small solitary asymptomatic nodules typically involving the face, head and neck areas with a male predilection. The incidence of chondroid syringomas varies from 0.01-0.098 percent. The preoperative diagnosis most often includes “tumor”, “nodule”, “cyst”, and “fibroma”. The mesenchymal component of mixed tumors often comprises a myxoid, chondroid, osseous, or a mixture of these...
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changes. However, large uniform vacuolated cells resembling lipomatous differentiation in the mesenchymal component have also been reported in pleomorphic adenomas and chondroid syringomas.\textsuperscript{1,4-11}

The origin of the lipomatous tissue has been under debate by various authors, but no definite answer has been established yet. It has been postulated by some authors that metaplasia of myoepithelial cells plays a role in the stromal differentiation of mixed tumors including the chondroid, osseous and lipomatous components.\textsuperscript{3,12-14} A study using pleomorphic adenomas as a model employing matrix gene expression concluded that epithelial-to-mesenchymal transdifferentiation represents the basic principle of the tissue heterogeneity in pleomorphic adenomas.\textsuperscript{15} They have also concluded that myoepithelial cell differentiation is only a minor cell differentiation pathway in pleomorphic adenomas.\textsuperscript{15}

Extensive lipomatous differentiation is a very rare finding in pleomorphic adenomas as well as chondroid syringomas with only a few case reports to date.\textsuperscript{1,4-11} This study was aimed to evaluate how often the lipomatous change happen in mixed tumors and attempt to elucidate the etiology of such changes via histopathological and immunohistochemical methods.

MATERIAL AND METHOD

Tissue preparation and histology

Previous cases diagnosed as mixed tumor of the skin in the past twenty years were retrieved from our archives and reviewed for lipomatous content. For fulfilling the diagnosis of chondroid syringomas the specimen must include an epithelial component and a mesenchymal component exhibiting either a myxoid, chondroid, osseous, or a mixture of these changes.\textsuperscript{1} Since there weren’t any universal criteria for diagnosing lipomatous mixed tumors (LMT) in terms of the amount of lipomatous component required, only cases with lipomatous content constituting larger than twenty percent of the total stromal component were included in our study. We believe that only well-developed lesions are suitable for studying the nature of LMT.

Immunohistochemical methods:

Previous authors have suggested that the myxoid and chondroid cells were modified or metaplastic myoepithelial cells in pleomorphic adenomas based on immunohistochemical and ultrastructural evidence.\textsuperscript{12-14,18-19} Sections were stained immunohistochemically for smooth muscle actin (SMA), glial fibrillary acidic protein (GFAP), and S-100 protein in an attempt to evaluate the relationship between epithelial, mesenchymal and lipomatous component of the tumors. The reagents used are detailed in Table 1.

RESULTS

Histopathological findings

Of the twenty-nine cases with cutaneous mixed tumors examined, varying degrees of lipomatous differentiation was noted in thirteen cases. Four out of the thirteen cases with lipomatous differentiation met the re-

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<th>Antigen</th>
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<td>M-0851</td>
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<td>GFAP</td>
<td>GA-5</td>
<td>1:100</td>
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quirement and were submitted for further examination.

All four tumors were well circumscribed exhibiting an epithelial component as well as a mesenchymal component. The epithelial component comprises sheets, nests, and strands of epithelial cells exhibiting glandular differentiation into ducts and tubules. Many of the epithelial cells were arranged in a disorderly fashion showing poor cohesiveness as they approached the border of aggregates. Clear cell change resembling trichilemmal differentiation was noted in one case. No other convincing evidence of follicular differentiation was noted. The stromal component showed fibromyxoid changes with focal hyalinization suggesting chondroid differentiation in one case. No osseous metaplasia was noted.

A large part of the stroma was composed of lipomatous tissue in all four cases (Fig 1). The lipomatous tissue were scattered throughout the tumor in nests and lobules partially separated by fibromyxoid septa. The lipomatous cells, when compared to normal subcutaneous lipocytes on the same section, showed a much greater variation in size ranging from small spindle cells with intracytoplasmic vacuoles to large mature-looking adipocytes. The nuclei of these adipocytes were not bizarre or atypical.

Much of the tumor featured areas in which transitional changes from epitheloid and tubular structures to fibromyxoid and lipomatous components were found. Solid areas of epithelial cells gave way to nests and cords with gradual accumulation of bluish mucin in the surrounding stroma. The epithelial cells detached from each other becoming polygonal cells or spindle cells scattered in the myxofibrous matrix (Fig. 2). Surrounding the lipomatous areas, many spindle cells had clear, variable-sized cytoplasmic vacuoles termed “intermediate cells” which seemed to establish histological continuity between the spindle cells and the adipocytes (Fig. 3). Intermediate cells were noted only in two of the four cases with extensive lipomatous content. They were not detected in mixed tumors with scarce lipomatous content.

**Immunohistochemical staining**

Staining for S-100 protein was positive...
When compared to the staining of the internal control fat tissue, stronger positivity was noted. Many of the spindle cells, intermediate cells and most of the small adipocytes in the transitional zone stained for S-100 protein (Fig. 4A).

SMA was strongly positive in a small number of outer cells of the tubules as well as in epitheloid cells forming nests and cords. Scattered positivity was noted in some polygonal cells, spindle cells as well as some of the intermediate cells (Fig. 4B). The more mature lipomatous cells and the inner cells of tubules were negative for SMA. Staining for GFAP was noted in a minority of outer cells and the epitheloid cells of nests and cords. Many of the polygonal cells and spindle cells were also positive for GFAP while no visible vacuolated spindle cells could be found with GFAP positivity (Fig. 4C). The more mature lipomatous cells were negative for GFAP.

**DISCUSSION**

Ongoing debate and research concerning the origin of mixed tumors has been noted from as early as 1859, when Billroth first characterized this entity as mixed tumor of the skin, believing that it was similar to pleomorphic adenoma of salivary origin. It was later coined as “chondroid syringoma” in 1961 by Hirsch and Helwig noting sweat gland elements in a chondroid stroma. The presence of lipomatous tissue in the stroma of mixed tumors of the skin was also mentioned in their study of 188 cases, but no theory as to its origin was proposed. Thirteen (45%) out of the twenty-nine cases reviewed in this article exhibited focal to diffuse lipomatous content close to the 44% incidence reported by Kazakov et al. Extensive lipomatous component in the stroma of mixed tumor was, to the best of our knowledge, first reported in 1995 by Ng et al., arising from the submandibular gland in a 35-year-old woman. Since then, six other cases of LMT
of the salivary gland as well as eight cases of the skin have been reported.\textsuperscript{1, 2, 4-11, 22} Four of our twenty nine cases showed extensive lipomatous content (14\%) as opposed to the much lower incidence rate of 1\% noted by Kazakov \textit{et al.}\textsuperscript{2} This substantial difference in incidence rate may be the result of the different criterion employed. The clear cells noted in our study possessed a round nucleus and were much smaller than the lipomatous cells. They were intermixed with the epitheloid cells in sheets and nests and surrounded tubular structures. They were thought to represent trichilemmal differentiation.\textsuperscript{2}

Differential diagnosis of LMT include lipomas with myxoid changes and spindle cell lipomas both of which do not exhibit the epithelial component of mixed tumors. Cutaneous adenolipomas are believed to result from entrapment of well differentiated eccrine glands and ducts by neoplastic adipose tissue.\textsuperscript{23} They should not be confused with LMT which aside from tubular structures, exhibit epitheloid cells in aggregates and cords throughout the tumor as well as spindle shaped cells in intermediate zones.

Mixed tumors are considered by some authors to be within the spectrum of myoepitheliomas. Lipomatous changes are also known to occur in myoepitheliomas.\textsuperscript{1} Several hypotheses attempting to explain the presence of adipose tissue in mixed tumors have been suggested. In normal tissue, increase of adipose tissue is often noted in older age groups, replacing the functioning units exemplified in hepatocytes, the glomerulus of the kidney, and parotid glands.\textsuperscript{8} It may be tempting to speculate that components in the mixed tumor may just undergo degeneration and is replaced by normal fat cells. However, the duration of the tumor in our cases ranged greatly from 2 months to decades and seemed to speak against the notion. Additionally, the “adipocytes” in lipomatous mixed tumors vary greatly in size and stain strongly for S-100 as compared to the uniform appearance and weaker S-100 staining in normal fat tissue, an observation noted in other

Fig. 4
(A) Staining of spindle cells and adipocytes. (S-100, original magnification x100)
(B) Focal staining of spindle cells and vacuolated cells. (SMA, original magnification x100)
(C) Focal staining of immature adipocytes and spindle cells. (GFAP, original magnification x100)
The possibility of stromal fat being entrapped during tumorigenesis has been suggested but was not persuasive since in our mixed tumors with extensive lipomatous content, the lipomatous tissue is not only centrally located but also diffusely distributed in the tumor. In addition, it was often the main component of the tumor surrounding the epithelial component instead.\(^4\)\(^5\)

Many recent studies concur that the mesenchymal component of mixed tumors arises from the epithelial component.\(^1\)\(^5\)\(^8\) A number of authors have attributed the various metaplastic spectrum of mixed tumors to metaplastic myoepithelial cells based on histological, immunohistochemical and ultrastructural findings.\(^1\)\(^2\)\(^4\)\(^-\)\(^1\)\(^4\)\(^5\) In our investigation, a transition zone between solid nests of epithelial cells and aggregated mature adipocytes was noted and described. It is in this area where we identified cells that were first called “intermediate cells” by Miracco \textit{et al.} and reported in various studies as well.\(^4\)\(^5\) These intermediate cells are typified by elongated, tapered nuclei with single or multiple vacuoles. In our study, staining for S-100 and SMA was often positive. Besides S-100 and SMA, positive staining for AE1/3, CK7, and CK14 was additionally noted in previous studies.\(^1\)\(^4\)\(^5\) Intermediate cells must be differentiated from adipocytes with Lochkern and lipoblasts. Lochkern and its variants, specifically Ringkern and Kerbnekern have been shown to exist in fat tissue, endothelia and smooth muscles of small vessels in the brain as well as the medulla.\(^2\)\(^4\) The intracytoplasmic vacuoles occurring in intermediate cells seemingly expand and compress the nucleus while the Lochkern are smaller and confined within the boundaries of the nucleus with the exception of the Kerbenkern which notches the nucleus instead of compressing it externally.\(^2\)\(^4\) Lipoblasts may also stain with S-100 as noted in liposarcomas,\(^2\)\(^5\) but they are not known to stain for SMA. The nuclei of lipoblasts in liposarcomas are more polymorphous and hyperchromatic. Moreover, mitosis has never been a feature of LMT.

Ultrastructural studies performed by Erlandson \textit{et al.}\(^1\)\(^8\) and Dardick \textit{et al.}\(^2\)\(^6\) traced the transition of the ductular myoepithelial cell from the periphery of the ducts to the myxoid and chondromyxoid regions of pleomorphic adenomas. Other ultrastructural studies identified single transitional cells containing lipid droplets, tonofilaments and myofilaments.\(^5\)\(^7\)\(^1\)\(^1\) Thus, we believe that these intermediate cells represent spindle shaped myoepithelial cells in the process of transdifferentiation.

In conclusion, lipomatous transdifferentiation in mixed tumors of the skin is a common event and when extensive, offers an excellent opportunity for researchers to search for its origin. Cells with myoepithelial differentiation play an important role in the transdifferentiation of lipomatous tissue in mixed tumors. Further research is required to elucidate the role of myoepithelial cells in the epithelial-mesenchymal transdifferentiation of mixed tumors.

REFERENCES
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脂肪性皮膚混合瘤

林鴻緯 劉漢南
國立陽明大學暨台北榮民總醫院皮膚部

背景：合併廣泛之脂肪性變化的皮膚混合瘤是一種甚少見於文獻記載的疾病。大部分的作者認為其脂肪變化是由腫瘤細胞本身變形生長而來的或是脂肪樣変性。
目標：本研究的目標為探討合併脂肪性變化的皮膚混合瘤之發生率並藉由病理學及免疫組織化學試圖找尋其發生原因。
方式：我們從過去二十年的病例檔案裡選出經病理切片診斷為皮膚混合瘤的病例，重新檢視並針對合併大量脂肪性變化的病例進行病理檢驗及對S-100蛋白、膠質纖維酸性蛋白、平滑肌肌動蛋白的特殊染色。
結果：我們一共分析了29個皮膚混合瘤的病例並且發現13例（45%）合併脂肪性變化，而其中4例（14%）則含有廣泛之脂肪性變化。較成熟的類脂肪細胞對S-100染色極為顯著而對平滑肌肌動蛋白、膠質纖維酸性蛋白染色則不明顯。在上皮與類脂肪區域交界處有發現一些“中間”細胞。
結論：合併脂肪性變化的皮膚混合瘤似乎並沒有想像中的罕見。S-100蛋白於脂肪樣變化處的強烈表現，與“中間”細胞的發現使我們認為變形生長是比較能解釋其來源。（中華皮誌：27: 85-92, 2009）