Primary Cutaneous Adenomyoepithelioma

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Abstract. Adenomyoepitheliomas are biphasic tumors composed of epithelial and myoepithelial components in varying proportions. They are commonly reported in the breast, uncommonly in salivary glands, and rarely in the lungs and vulva. Recent molecular analysis has shown that p27/kip-1 protein may play a role in their development. Primary cutaneous adenomyoepithelioma is an extremely rare tumor with only three well documented cases reported to date. We report a case of primary cutaneous adenomyoepithelioma with histological and immunohistochemical characterization, and discuss their differential diagnosis, biologic behavior and treatment strategies.

Introduction

Adenomyoepitheliomas (AMEs) are rare, biphasic tumors that exhibit epithelial and myoepithelial components in varying proportions [1]. They are more common in breast tissue. In regards to the skin, there are three well-documented cases of adenomyoepithelioma reported in the English literature [2,3,4]. In this article, we report another case of AME, arising primarily in the skin with a detailed light microscopic and immunohistochemical description, and discuss their biologic behavior, differential diagnosis, recently described molecular studies, and therapeutic options.

Case Report

A 45-year-old female presented with a fifteen year history of a painless mass on her upper mid back. Clinical impression was a cyst. A complete excision of the lesion was performed. The hematoxylin and eosin stained sections revealed a 2.5x2.0-cm, well-circumscribed, lobulated, dermal neoplasm **(Figure 1)**. Focal areas of retraction were noted between the tumor and the surrounding dermis. The lobules were composed of multiple, small, closely packed ductules separated by spindle and polygonal myoepithelial cells **(Figure 2A)**. Cuboidal cells with ample pink cytoplasm lined the ductules **(Figure 2B)**. Some ductules demonstrated a prominent pink hyaline reduplicated basement membrane that separated the myoepithelial cells, and a few ductules contained pink secretions in their lumens. Occasional dilated ducts were also noted. A few foci of squamous metaplasia and calcifications within the ductules were identified **(Figure 2A)**. The ductules were surrounded and separated by mixed polygonal and spindle-shaped myoepithelial cells **(Figure 3)**. In areas with myoepithelial overgrowth, the ductules were compressed with luminal obliteration. The myoepithelial cells demonstrated a fascicular pattern in the spindle cell rich areas **(Figure 3)**. The myoepithelial cells had clear cytoplasms and bland, oval to spindle nuclei **(Figures 4A and 4B)**. No infiltrating growth pattern, nuclear pleomorphism, atypical mitosis, or necrosis was observed in the tumor. The light microscopic findings of the two distinct cellular populations in the tumor were confirmed by immunohistochemical analysis. The glandular cells stained positively with various cytokeratin antibodies such as AE1/3, CK5/6, CAM 5.2 and CK7 **(Figure 5A)**. EMA stained the luminal portions of the ductules **(Figure 5B)**. The myoepithelial component demonstrated a strong reaction for S-100 protein **(Figure 5C)** and calponin **(Figure 5D)** and a weak reaction with smooth muscle actin. Desmin and muscle specific actins were negative.

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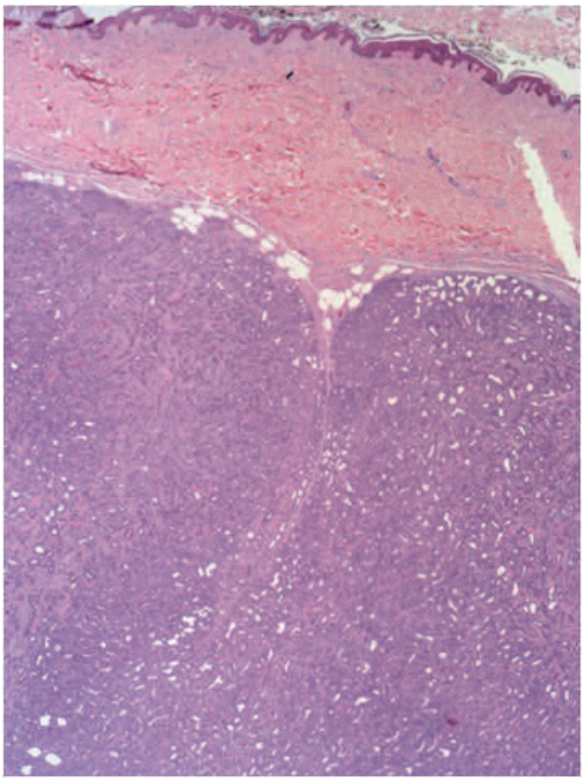

Figure 1. *Low power magnification of the AME showing a well circumscribed lobulated tumor in the dermis, upper portion of the tumor. There was no infiltrating tumor noted. Hematoxylin and Eosin stain, original magnification x50.*

Discussion

Adenomyoepitheliomas (AMEs) are biphasic tumors that exhibit epithelial and myoepithelial components [1]. They are also called epithelial-myoepithelial tumors in other organs. They are seen in patients of all ages. Most cases are reported in the breast [1,5]; however a few cases have occurred in the salivary glands, lungs and vulva [6,7]. These tumors are rare in the skin, with only three well documented cases reported in English literature [2,3,4].

Histologically, AMEs are mostly well circumscribed tumors composed of glands/ductules surrounded by a variable amount of myoepithelial cell proliferation. Cuboidal cells line the glandular units, whereas the myoepithelial cells are either polygonal or spindle-shaped with eosinophilic or clear cytoplasms [1]. AMEs are classified as tubular, lobulated, or spindle cell types, based on their growth pattern and cell morphology [1]. The most common microscopic pattern is the tubular type that shows tubules, glands, and/or ducts separated by islands and bands of myoepithelial cells that exhibit clear cytoplasm [1]. In some lesions, strands of pink, hyalinized basement membrane and stroma separate myoepithelial cells. Apocrine metaplasia is common, whereas squamous and sebaceous

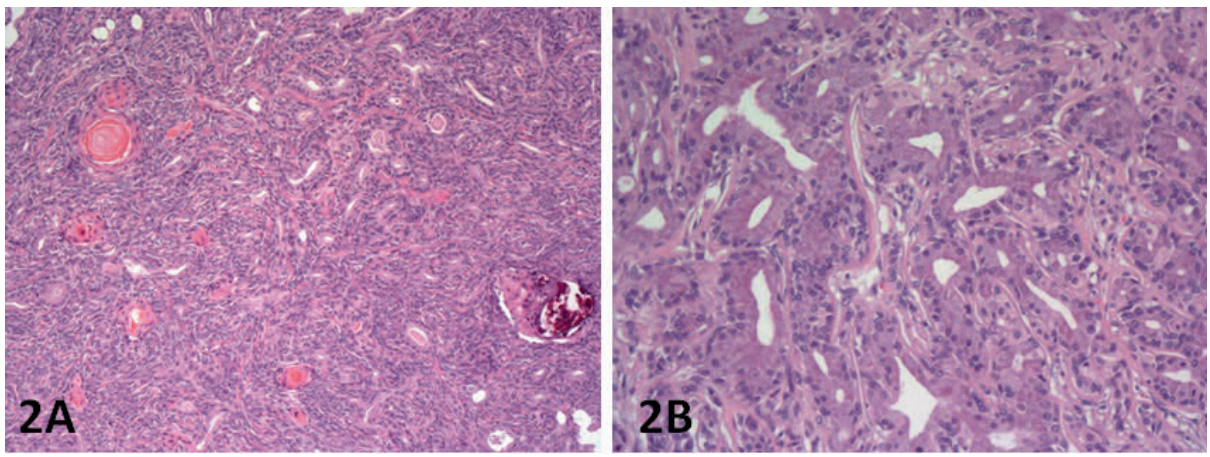

Figure 2. ***A.*** *AME showing multiple small ductules some with secretions in the lumina. The ductules are separated by myopeithelial cells. Also note the squamous metaplasia and calcification involving some ductules. Hematoxylin and Eosin stain, original magnification x 250.* ***B.*** *Higher magnification showing back to back placed multiple ductules lined by high cuboidal cells with ample pink cytoplasm. Note pink reduplicated basement membranes surrounding many ductules. Hematoxylin and Eosin stain, original magnification x 500.*

metaplasias are rare [8]. Calcifications are occasionally present in the glandular lumens. Due to the large nature of some tumors, central fibrosis and/or necrosis secondary to infarction are not uncommon findings. At times, the myoepithelial proliferation can be more pronounced than the glandular elements. Atypical features such as scattered mitotic figures, focal mild nuclear pleomorphism and hyperchromasia, and occasional multinucleated cells can be seen in the tumor [9]. The presence of these atypical histological features should be interpreted with caution and must be included in the pathology report. Malignant degeneration in AME is a rare event. Malignant change involves the epithelial component more often than the myoepithelial cells [9-11].

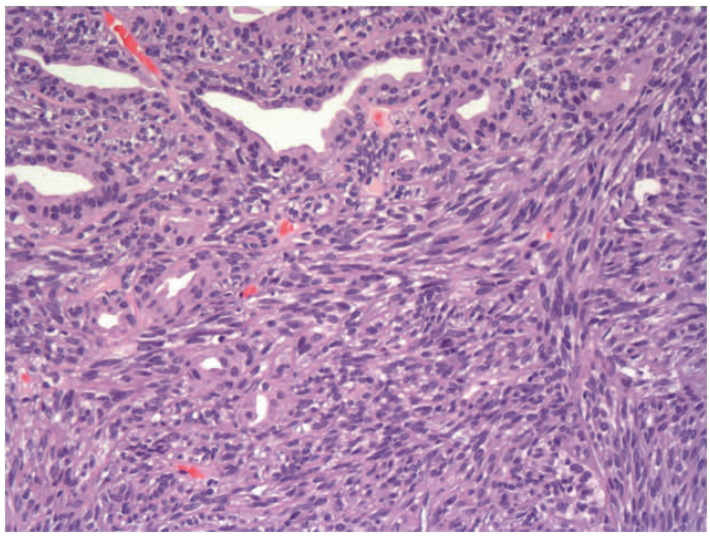

Figure 3. *The ductules are separated by polygonal and spindle myoepithelial cells. In areas of myoepithelial overgrowth the spindle myoepithelial cells are arranged in fascicles. Hematoxylin and Eosin stain, original magnification x 250*

Features suggestive of malignant transformation include infiltrating borders, hypercellularity, myoepithelial overgrowth, prominent cellular atypia, nuclear pleomorphism, necrosis, and a high mitotic rate [9-11]. Histologically, benign appearing AME of the breast with lung metastasis has been reported in two cases [12].

The immunohistochemical profile of AME is irrespective of the site of origin and is summarized in **Table 1**. The glandular/ductular cells exhibit a strong reactivity with antibodies to various cytokeratins (AE1/3, CK-5/6, CAM 5.2, CK 7) with their luminal surfaces (cuticles) exhibiting a positive reaction with epithelial membrane antigen (EMA). The ductular cells in AMEs are mostly

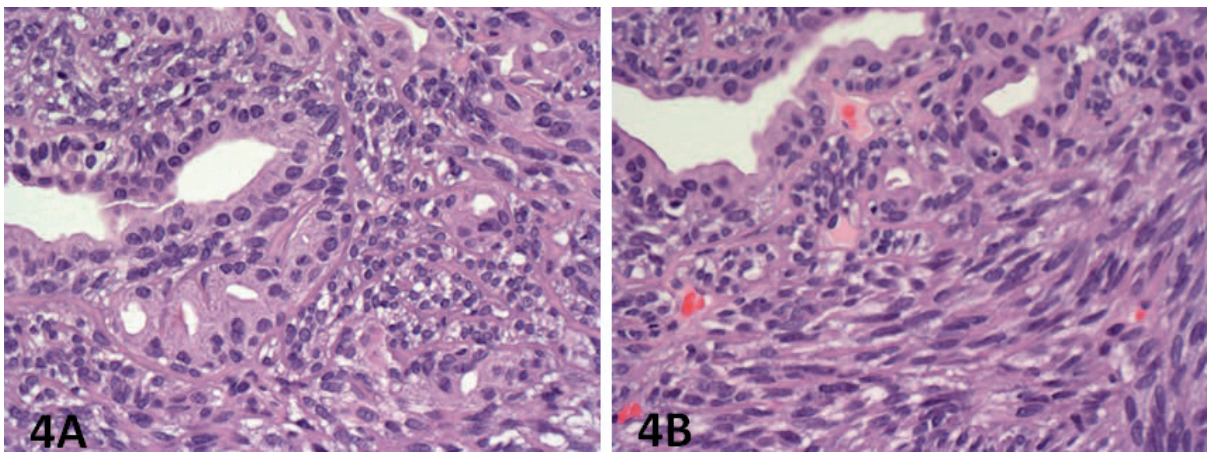

Figure 4 . A. *Higher magnification of myoepithelial cells. Polygonal cells with oval nuclei and clear cytoplasm and* ***B.*** *spindled cells with elongated nuclei and pink to clear cytoplasm. Hematoxylin and Eosin stain, original magnification x 500*

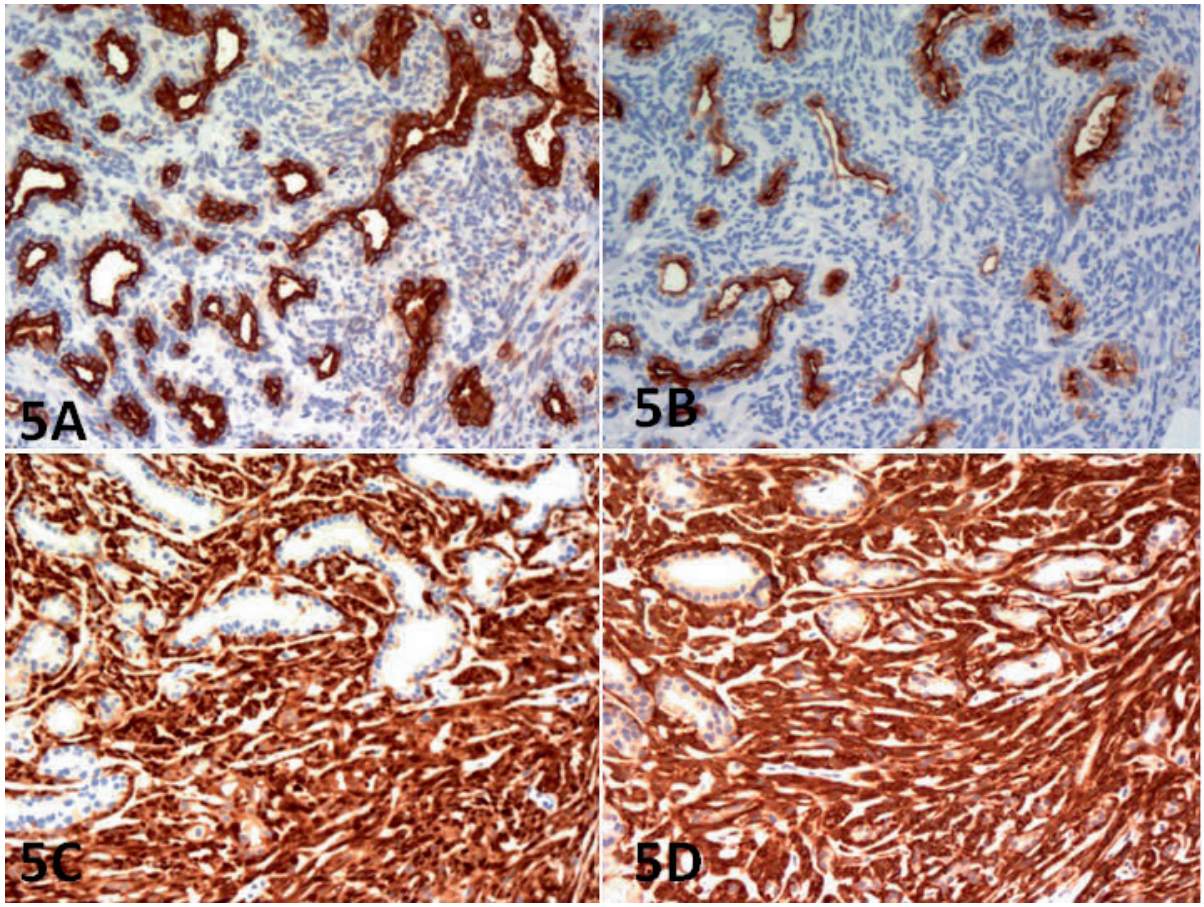

Figure 5. A. *Immunohistochemical profile of the AME. Cytokeratin, CK-7 staining only the ductules;* ***B.*** *Epithelial membrane antigen staining the luminal surfaces of the ductules;* ***C.*** *S100 stain with positive reaction only in the myoepithelial cells;* ***D.*** *Calponin immunostain showing a strong positive reaction in the myoepithelial cells.*

S-100 negative. The polygonal and spindle myoepithelial cells are usually reactive to calponin, alpha smooth muscle actin, desmin, p63, calponin, variably reactive to low molecular weight cytokeratins, and non reactive to EMA. A subset of myoepithelial cells can be S-100 positive, but its intensity and uniformity of reactivity varies considerably. Actin staining tends to be more conspicuous in the spindle cell component. Immunohistochemical stains that are relatively specific for myoepithelial cells, including alpha smooth muscle actin, calponin, p63, and maspin, can be expressed in these tumors [13]. P63 staining is specifically helpful because of its nuclear localization that precludes cytoplasmic cross reactivity in myofibroblasts that can occur sporadically with other myoepithelial markers. The immunophenotype of neoplastic myoepithelial cells can, at times, be different than their normal counterpart, and a panel of immunostains should be utilized to detect their presence. CD10 represents a non specific maker that can show a positive reaction in the myoepithelial cells.

Cutaneous AME shares the same histopathologic features as its breast counterpart and must satisfy the same histological criteria for its diagnosis [1]. For its diagnosis, primary cutaneous AME must exhibit both myoepithelial and ductular components with the myoepithelial component comprising at least 25-50% of the tumor. The myoepithelial cells can be either polygonal or spindle cells with clear or eosinophilic cytoplasm. The epithelial components, composed of ductules, are lined by cuboidal to columnar cells and often show apocrine differentiation. In areas with myoepithelial overgrowth, the ductules are compressed and pushed to the edge of the tumor. Both components should be cytologically bland with minimal to absent nuclear pleomorphism and a low mitotic rate. Rare findings of central necrosis and dystrophic

Table 1. *Immunohistochemical profile of Adenomyoepithelioma*

Antibody	Epithelial Component	Myoepithelial Component
AE1	+	±
AE3	+	±
CK7	+	-
CK5/6	+	±
CAM 5.2	+	-
Epithelial membrane antigen	+	-
Calponin	-	+
S100	-	±
P63	-	+
Smooth muscle actin	-	+
CD10	-	+
Maspin	-	+
Smooth muscle myosin	-	-
Desmin	-	-

calcifications are allowed in larger tumors, but atypical features should be interpreted with great caution.

Similar to AME in other sites/organs, primary cutaneous AME should probably be regarded as a low grade tumor with borderline malignant potential. Their biologic behavior, prognosis and treatment is similar to its breast counterpart [14]. Although the majority of the tumors are considered benign and treated as such, they can be locally aggressive with a propensity for local recurrence. Incomplete excision, removal with narrow margins, tubular variants, and some lobular tumors with high mitotic activity are at risk for higher local recurrences and therefore, a wide excision with liberal margins of such tumors is recommended [5,14].

Recently, a few authors have shown that the p27/kip-1 protein plays a fundamental role in the development of these neoplasms [15]. Protein p27/kip-1 is a cyclin dependent kinase inhibitor that blocks the cell cycle in the G0 and G1 phase and is abundant in the resting myoepithelial cells. Its expression inhibits and controls the progression of the cell cycle; therefore, it most likely acts as a tumor suppressor gene. Based on these observations, these authors have concluded that decreased or absent expression of this protein in the myoepithelial cells leads to their proliferation and development of an adenomyoepithelioma. In addition, a few authors hypothesize that this protein might also function as an oncogene. Further research on this protein and probable other related genes might help us better understand the origin and progression of these tumors.

Cutaneous AME should be differentiated from other skin tumors such as spiradenoma, tubular apocrine adenoma, mixed tumor, hidradenoma, dermal duct tumor, glomus tumor, myoepithelioma, and carcinosarcoma. Spiradenoma and AME can appear as dominant "blue balls in the dermis" under scanning magnification. However, a closer view of spiradenoma reveals tightly packed, back to back ductules lined by dark and clear cells and many pink reduplicated basement membranes. The tumor completely lacks a myoepithelial proliferation. Tubular apocrine adenoma predominantly shows tubules and glands of varying sizes with multiple papillary infoldings and luminal eosinophilic secretions, but it also lacks the polygonal or spindle cell myoepithelial component. Mixed tumors (chrondroid syringomas) can exhibit variable cellularity and tissue components, but mostly demonstrate well formed glands and ductules lined by cuboidal cells and polygonal myoepithelial cells with pink or eosinophilic cytoplasms, typically in a hyalinized or chondromyxoid stroma: a feature that is not observed in AME. Hidradenoma shows multiple dermal nodules composed of uniform sized, polygonal, ductal cells with

distinct cytoplasmic borders and moderate to abundant eosionophilic and/or clear cytoplasm. Dilated ductules with secretions, hyalinized, reduplicated, basement membrane, cystic degeneration is commonly noted. However, these tumors also lack the myoepithelial component. Dermal duct tumor demonstrates dermal nodules composed of small, uniform, poroid cells with scant cytoplasm showing occasional ductular differentiation and a complete absence of myoepithelial proliferation. Cutaneous myoepithelioma is composed of varying proportions of spindle, epitheliod and plasmacytoid myoepithelial cells and lacks epithelial component, but it can show focal ductal differentiation. Carcinosarcomas are large tumors that contain different types of epithelial and mesenchymal components that frequently exhibit an infiltrative growth pattern with marked cellularity, cytologic atypia, atypical mitosis, and tumor necrosis; they most likely represent sarcomatous or metaplastic carcinomas.

In conclusion, primary cutaneous AMEs are rare tumors with only three cases reported in English literature. They are characterized by a biphasic proliferation composed of epithelial elements in the form of multiple ductules mixed intimately with a varying density of spindle or polygonal myoepithelial cells. These tumors should be considered within the same spectrum/category of mixed tumors of the skin and should be regarded as their rare variant. [1]The term AME should be reserved for tumors demonstrating both components, with the myoepithelial component comprising at least 25-50% of the tumor. Given its rare occurrence in the skin, the biologic behavior and the treatment should be managed similar to its breast counterpart.

References

1. Tavassoli FA. Myoepithelial lesions of the breast. Myoepitheliosis, adenomyoepithelioma and myoepithelial carcinoma. *Am J Surg Pathol* 1991;15:554-68.
2. Hartz PH. Adenomyoepithelioma of sweat gland. Report of case. *Am J Clinic Pathol* 1946;16:385-9.
3. Clarke KE, Seykora JT. Primary cutaneous adneomyoepithelioma. *J Cut Pathol* 2007;34:654-7.
4. Wallis NT, Banerjee SS, Eyden DP, Armstrong GR. Adenomyoepithelioma of the skin: a case report with immunohistochemical and ultrastructural observations. *Histopathology* 1997;31:374-7.
5. Howlett DC, Mason CH, Biswas S, Sangle PD, Rubin G, Allan SM. Adenomyoepithelioma of the breast: Spectrum of disease with associated imaging and pathology. *Am J Radiol* 2003;180:799-803.
6. Tsuji N, Tateishi R, Ishiguro S, Terao T, Higashiyama M. Adenomyoepithelioma of the lung. *Am J Surg Pathol* 1995;19:956-62.
7. Ren J, Song L, Dang Q, Zhang X, Jiang S, Zhang G, Wang N, Liu Z, Wang J, Hwa YL, Li Z, Zhao X, Liu Y. Primary adenomyoepithelioma of tonsil. *Head and Neck Oncol* 2010;2:7.
8. Cai RZ, Tan PH. Adenomyoepithelioma of the breast with squamous and sebaceous metaplasia. *Pathology* 2005;37:557-9.
9. Built P, Verwiel JMM, Wobbes T, Kooy-Smits MM, Biert J, Holland R. Malignant adenomyoepithelioma of the breast with metastasis in the thyroid gland 12 years after excision of the primary tumor: a case report and review of the literature. *Virchows Arch* 2000;436:158-66.
10. Pauwels C, de Potter C. Adneomyoepithelioma of the breast with features of malignancy. *Histopathology* 1994;24:94-6.
11. Michal M, Baumruk L, Burger J, Manhalova M. Adenomyoepithelioma of the breast with undifferentiated carcinoma component. *Histopathology* 1994;24:274-6.
12. Nadelman, Celina M. "Benign", metastasizing adenomyoepithelioma of the breast: A report of 2 cases. *Arch Pathol Lab Med* 2006;130:1349-53.
13. Mentzel T, Requena L, Kaddu S, Soares de Aleida LM, Sangueza OP, Kutzner H. Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. *J Cut Pathol* 2003;30:294-302.
14. Loose JH, Patchefsky AS, Hollander IJ, Lavin LS, Cooper HS, Katz SM. Adenomyoepithelioma of the breast: a spectrum of biologic behavior. *Am J Surg Pathol* 1992;16:868-76.
15. Munoz G, Felipo F, Marquina I, Del Agua C. Epithelial-myoepithelial tumor of the lung: a case report referring to its molecular histogenesis. *Diagnostic Pathol* 2011;6:71.