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Clinical and pathological study on mixed tumors of the skin

Huiying Wan, MD[a], Minyan Xu, BS[a], Tian Xia, BS[b,*]

Abstract

Mixed tumor of the skin (MTS) is a rare benign tumor of the sweat glands with a reported frequency of 0.01% to 0.098%. The objective of the study is to investigate clinicopathological and immunohistochemical features of mixed tumor of the skin.

This was a retrospective study of 21 patients diagnosed with MTS at the Institute of Dermatology and Venereology of Sichuan Provincial People's Hospital from 1980 to 2016. Pathological sections of all cases were reread and the diagnosis was verified.

There were 14 males (67%) and 7 females (33%). MTS affected the face. The lesions were skin-colored or lightly red, with no subjective symptoms in most cases. Histopathologically, the tumors consisted of epithelial and interstitial components. The epithelium was mainly composed of cubic or polygonal cells, which can be seen within the tubule-like structures with bilayer epithelium. The inner cells mainly expressed cytokeratin and other epithelial markers. The outer cells expressed epithelial and mesenchymal markers. The outer cells expressed S-100, P63, and glial fibrillary acidic protein. The tumors showed interstitial mucus-like and fibrosis changes, and some parts had cartilage-like changes.

Pathological diagnosis is particularly important because the clinical symptoms of MTS lack specificity.

Abbreviations: CEA = carcinoembryonic antigen, CK = cytokeratin, EMA = epithelial membrane antigen, GFAP = glial fibrillary acidic protein, H&E = hematoxylin-eosin, MTS = mixed tumor of the skin, MXB = maixin biotechnologies, PCNA = proliferating cell nuclear antigen, PLAG = pleomorphic adenoma gene, SMA = smooth muscle actin, ZSJQ = ZhongShanJinQiao.

Keywords: benign tumor, chondroid syringoma, immunohistochemistry, mixed tumor of the skin, pathology

1. Introduction

Mixed tumor of the skin (MTS) is a rare benign tumor of the sweat glands with a reported frequency of 0.01% to 0.098%.[1–5] MTS is also known as chondroid syringoma. MTS is non-ulcerating, slow-growing, subcutaneous, dermal nodules, and occur in adults in the head and neck area despite the fact that malignant mixed tumors are usually more common on the trunk and extremities.[1,6,7] Men are more often affected than women.[1,7,8] Because of its rarity, it is easy to clinically misdiagnose MTS. Pathologically, MTS shares some features with pleomorphic adenomas (or salivary gland mixed tumors).[9,10] MTS was composed of both epithelial and mesenchymal components and was characterized by sweat gland elements in a cartilaginous stroma.[6,11] MTS is usually benign, but some even rarer cases of malignant MTS have been reported and associated with local recurrence, metastases, and mortality.[12,13]

The optimal treatment for MTS is complete excision.[1,3,14,15] Cytology of material obtained by fine needle aspiration could provide some clues about the nature of the tumor, but the definitive diagnosis has to be made on the surgical specimen.[3,14] Since the tumor is often lobulated, achieving margins in normal tissues is often necessary.[9]

In this retrospective study, 21 patients with benign MTS were included. The clinicopathological characteristics of the patients were analyzed and compared with the literature.

2. Methods

2.1. Study design and patients

This was a retrospective study of 21 patients diagnosed with MTS at the Institute of Dermatology and Venereology of Sichuan Provincial People's Hospital from 1980 to 2016. The study was approved by the ethics committee of the Sichuan Provincial People's Hospital. The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were: diagnosis of MTS; complete clinical information; and sufficient tissue for pathological analyses. The patients were identified using the hospital records and the clinical data. Films of pathological sections of all cases were reread and the diagnosis was verified. The diagnostic criteria of MTS was made according to established diagnostic criteria[6,16,17]: tumor located in deep dermis or subcutaneous fat layer; tumor cells consisted of epithelial and interstitial components; the epithelial component was composed of cubic or polygonal cell nests or cellular band, and some formed cystic

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Table 1

Characteristics of the 21 cases of mix tumor of the skin.

Gender (male/female)	14:7
Age, y	
Age range	21–75
Average age	45.7
Median	42
Onset part (cases)	
Nose	10
Cheek	4
Upper lip	4
Eyelid	1
Arcus superciliaris	1
Chin	1
Growth time, mo	
Range	2–120
Average	17.6
Median	10
Size, mm	
Range	5–20
Average	14
Median	12

cavity; lumen and cystic cavity were lined with 2 layers of epithelial cells; the outer layer was flat cells, while the inner layer was cubic cells; and interstitial component included cartilage-like, mucus-like, and fibrous components.

2.2. Pathological and immunohistochemical analysis

Specimens were tumor tissues resected by surgery, fixed with 10% formalin. Then, routine sample collection, dehydration, and embedding with paraffin were performed. Wax blocks were extracted and sliced into 4-μm sections. The sections were stained with hematoxylin-eosin (H&E) and observed. The primary antibodies for immunohistochemistry included actin, desmin, Ki-67, epithelial markers (including cytokeratin (CK), CK5/6, CK8, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA)) and mesenchymal and myoepithelial markers (including Vimentin, glial fibrillary acidic protein (GFAP), smooth muscle actin (SMA), S-100, and P63). Related antibodies were provided by Maixin Biotechnologies (MXB) (Fujian, China) and ZhongShanJinQiao (ZSJQ) Biotechnologies (Beijing, China) (Supplemental Table S1, http://links.lww.com/MD/C456). Positive tissue sections were used as positive controls. Films of the pathological sections were read by 2 pathologists, including 1 chief pathologist and 1 deputy chief pathologist. Positive results were judged according to the presence of brown yellow granular staining in the cytoplasm, cell membrane, or nuclei.

2.3. Statistical analysis

Only descriptive statistics were used.

3. Results

3.1. Clinical characteristics of the patients

All cases had sufficient specimens and were pathologically diagnosed with MTS. None of the cases was excluded due to incomplete information or specimen. Table 1 presents the characteristics of the patients. There were 14 males and 7 females. The age at onset was 21 to 75 years (mean, 45 years). Clinical manifestations were the occurrence of hemispherical or round nodules on the skin. Disease history was 2 months to 10 years. All the skin lesions occurred on the face, including 10 cases on the nose, 4 on the cheek, 4 on the upper lip, 1 on the eyelid, 1 on the arcus superciliaris, and 1 on the chin. All the cases developed a single nodule, manifesting as isolated hemispherical, or round nodule that grew slowly. The nodules slightly bulged from the surface of the skin with a long-axis diameter of 0.5 to 2 cm. The boundary of the nodules was clear, and the surface of the nodules was smooth and without ulceration (Fig. 1A). The color of the surface of the nodules was mainly skin-colored or lightly red, and there were no obvious subjective symptoms. The section of tumors was grayish white and solid (Fig. 1B). Honeycombs or cavity-like changes were visible in 3 cases.

3.2. Microscopic examination

Table 2 presents the pathological characteristics of the MTS. At low magnification, the epidermis was basically normal and the tumors were located in the dermis or subcutaneous fat layer with clear boundary. Tumors consisted of epithelial and interstitial components. The morphology and arrangement of tumors were diverse. Epithelial cells were mostly cubic or polygonal, and nuclei were round or oval. There were branching ducts within the tumors. Lumen sizes and shapes varied greatly, and some formed cystic cavity. Lumen and cystic cavity were lined with 2 layers of

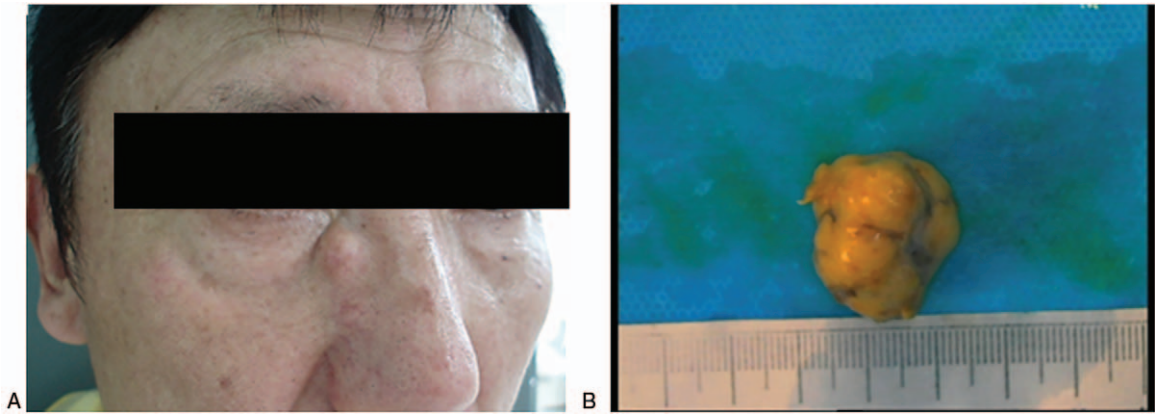

Figure 1. Gross examination of a mixed tumor of the skin. A, Hemispheric nodules on the nose, which were skin-colored with a smooth surface. B, Gross pathological examination showed that the tumor was complete and with clear boundary.

Table 2

Pathological microscopic features of the 21 cases of mixed tumor of the skin.

Features	Number of cases (%)
Components	
Epithelial cells	5 (23.8)
Mesenchymal cells	3 (14.3)
Mixed type	13 (61.9)
Parts	
Dermis only	7 (33.3)
Subcutaneous only	4 (19.0)
Involvement of dermis and subcutaneous	10 (47.7)
Boundary	
Clear	21 (100)
Main epithelial structures	
Cubic, polygonal epithelium	21 (100)
Branching tubular structure	21 (100)
Formation of cystic cavity	4 (19.0)
Epithelial cell nest	21 (100)
Single epithelium	16 (76.2)
Plasmacytoid cells	6 (28.6)
Main interstitial structures	
mucus-like interstitium	16 (76.2)
Fibrous interstitium	11 (52.4)
Cartilage-like interstitium	5 (23.8)

epithelial cells. The lumen surface showed cubic cells and the outer layer was flat cells. Some epithelial cell masses and single epithelial cell were scattered in the interstitium. The interstitium was mainly mucus-like interstitium, while some cartilage-like changes can be seen (Fig. 2).

Two histopathologic subtypes have been observed. The MTS of apocrine origin has relatively large and irregular tubule lumen. The tubules are composed of an outer myoepithelial cell layer and an inner epithelial cell layer, the latter often manifesting apocrine secretion. The MTS of eccrine origin characteristically has ducts lined by a single layer of flattened, cuboidal epithelial cells. Those of ducts are small, round, or linear, with relatively uniform morphology, no branches, and evenly distributed in mucus-like interstitium and cartilaginous stroma. Among them, 17 cases (81.0%) were apocrine MTS, while 4 (19.0%) were eccrine MTS.

Tumors consisted of epithelial and interstitial components in different proportions. Five cases (23.8%) mainly consisted of epithelial component. Epithelial component mainly included apocrine sweat gland, eccrine sweat gland, sebaceous gland, and hair. Three cases (14.3%) mainly consisted of mesenchymal component, including mucus-like, fibrous, and cartilage-like matrixes. Thirteen cases (61.9%) were composed of mixed epithelial and mesenchymal components. A majority of tumors consisted of 1 or more than 2 matrix types. Among them, 16 cases (76.2%) showed myxoid matrix, 11 cases (52.4%) showed fibrous matrix, and 5 cases (23.8%) showed cartilage-like matrix. There were 21 cases (100%) with gland ducts, and the lumen cavity contained eosinophilic amorphous substances. Plasmacytoid cells were observed in 6 cases (28.6%). All tumors had complete capsule.

3.3. Immunohistochemistry

Tables 3 and 4 present the immunohistochemical characteristics of the tumors. The inner epithelial cells mainly expressed epithelial markers (Fig. 3A–C), including CK, CK5/6, CK8, EMA, and CEA, but they did not express mesenchymal and myoepithelial markers. The outer epithelial cells expressed not only epithelial markers, but also most mesenchymal and myoepithelial markers, including Vim, S-100, GFAP, SMA, and P63. Among them, the proportions of Vim, S-100, and P63 were higher (Fig. 3D–G). Nested epithelium and scattered epithelial masses were similar with the same immunohistochemical expression pattern as the outer epithelial cells. Plasmacytoid cells were observed in 6 cases, which were mainly CK positive and Vim positive (Table 3). Markers of the interstitial components were mostly negative, with varying degrees of Vim expression (Fig. 3H). There was a certain proportion of S-100 expression in cartilage-like interstitium (Table 4). Des and Actin were all negative in the epithelium and interstitium, while other markers only appeared in outer epithelial cells. Positive rate of Ki-67 was very low.

4. Discussion

MTS is a rare benign tumor of the sweat glands with a reported frequency of 0.01% to 0.098%. The aim of this study was to investigate clinicopathological and immunohistochemical features of mixed tumor of the skin. The results suggest that pathological diagnosis is particularly important because the clinical symptoms of MTS lack specificity.

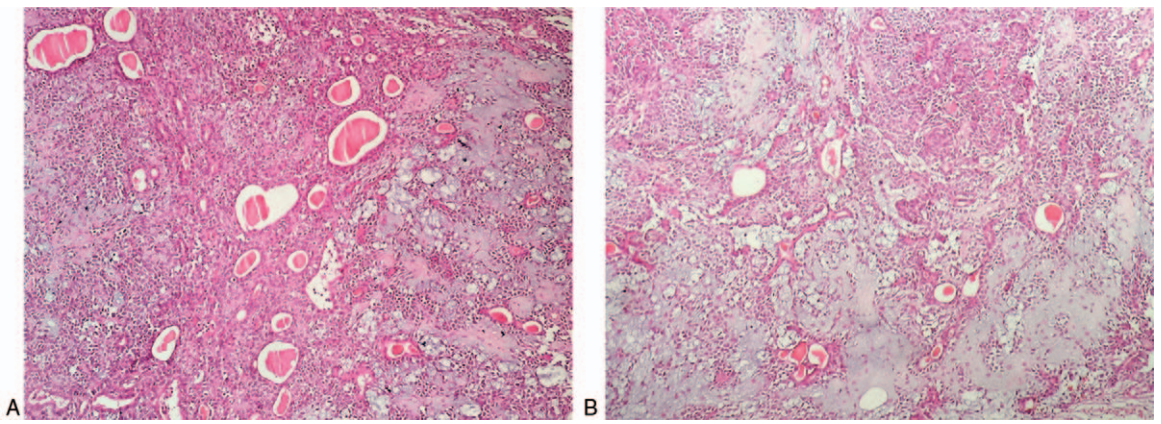

Figure 2. Microscopic examination of different parts of a mixed tumor of the skin. A, Presence of lumen-like epithelium and interstitium (HE, ×100). B, Mucus-like interstitium and local cartilage-like changes (HE, ×100).

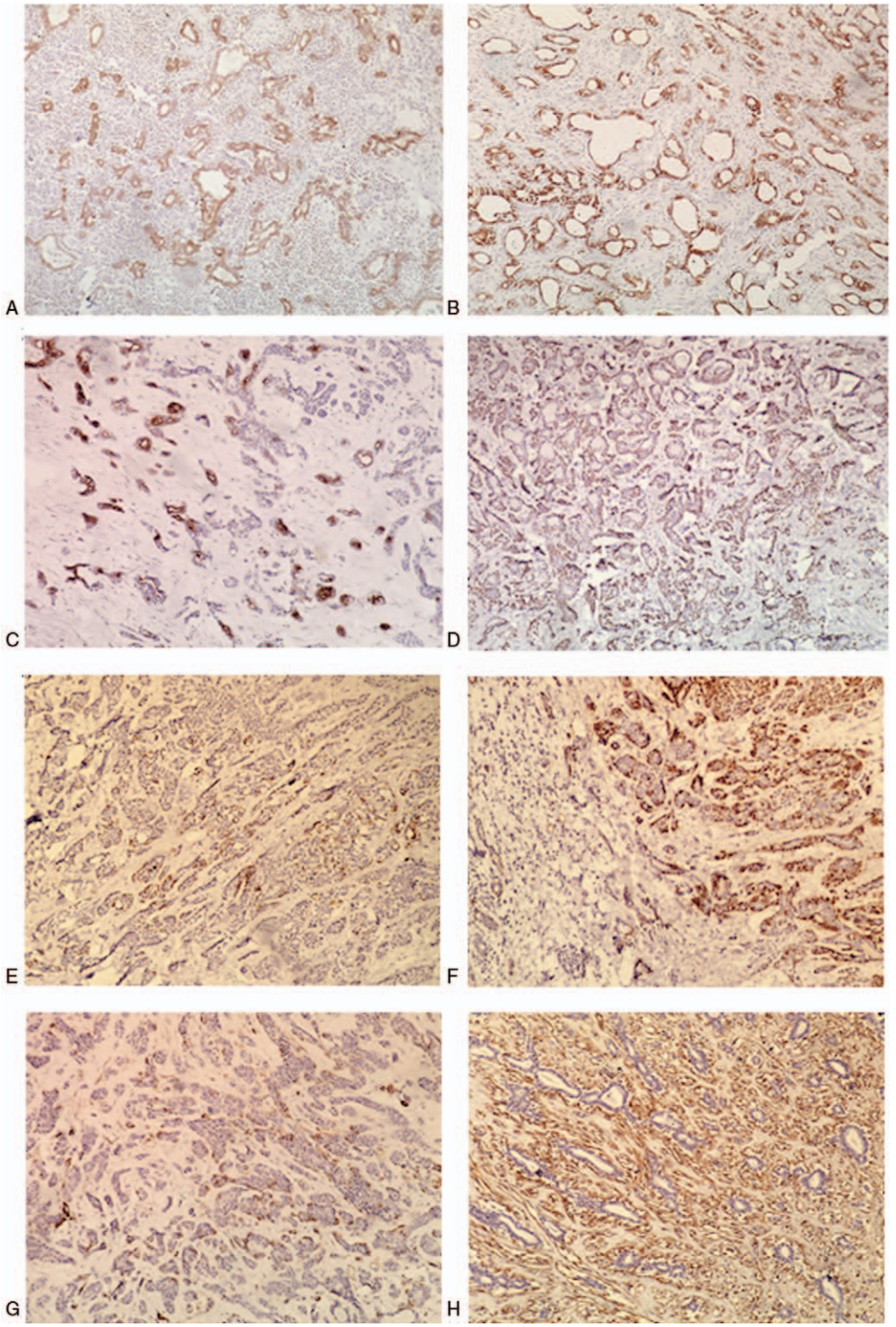

Figure 3. Immunohistochemistry of different parts of a mixed tumor of the skin. A, Positive expression of CK in epithelial cells (SP, ×100). B, Positive expression of CK8 in epithelial cells (SP, ×100). C, Positive expression of CEA in inner epithelium (SP, ×100). D, Positive expression of P63 in outer epithelial nests (SP, ×100). E, Positive expression of GFAP in outer epithelium (SP, ×100). F, Positive expression of S-100 in outer epithelium and epithelial nests (SP, ×100). G, Positive expression of SMA in outer epithelium and epithelial nests (SP, ×100). H, Positive expression of Vim in outer epithelium and interstitium (SP, ×100). CEA = carcinoembryonic antigen, CK = cytokeratin, GFAP = glial fibrillary acidic protein, SMA = smooth muscle actin.

MTS is also known as chondroid syringoma, which is a rare and usually benign tumor of the skin. Billroth proposed the definition of benign MTS in 1859.[18] The literature reports that the incidence of MTS accounts for 0.01% to 0.098% of primary skin tumors and maybe even less.[1–4] MTS usually occurs in middle-aged men, predominantly on the head and neck.[1,6–8] Clinical features of MTS are a single subcutaneous nodule with slow growth and clear boundary.[1,6,7] The nodules are medium hard or hard in texture, which is considered to be related to their interstitial component.[6,11] Diameters of the masses are mostly

Table 3

Immunohistochemistry for the 21 cases of mixed tumor of the skin.

	CK	CK5/6	CK8	EMA	CEA	Vim	S-100	GFAP	Des	Actin	SMA	P63	Ki-67*
Inner epithelium	21	20	21	21	17	0	2	0	0	0	0	0	2%
Outer epithelium	21	17	12	7	1	21	21	16	1	2	14	21	1%
Epithelial nest	20	14	12	9	2	12	15	8	0	1	11	16	1%
Plasmacytoid cells†	6	2	3	5	2	6	4	2	0	0	4	2	1%

* Ki-67 is an index of positive rate, and the data is shown as the number of positive rate of the enrolled cases.
† There were 6 cases of plasmacytoid cells.

0.5 to 3 cm, but tumors of up to 9 cm have been reported.[19] The tumors are smooth in surface, which are mostly light red or skin-colored. Furthermore, there is basically no ulceration.[1,6,7]

Histological manifestations of MTS are various, but they mainly manifest as epithelial components embedded in a mucus-like, cartilage-like, or fibrous matrix.[20] MTS can be divided into apocrine MTS and eccrine MTS. Under the microscope, apocrine MTS have relatively large tubule lumen. The lumen wall is covered by 2 layers of cells, there are branch ducts, and apocrine secretion is visible, suggesting that there is apocrine differentiation. Eccrine MTS consists of relatively small round gland ducts without branches and apocrine secretion. Besides the above 2 main adenoid structures, there are also solid epithelial bands, epithelial islands, and single epithelial cells. Some cases develop hair follicle differentiation with visible hair germ cells or sebaceous gland cells. Most of the cases with these changes are apocrine MTS.[11] Some cases have hair matrix differentiation, eosinophilic ghost cells, and giant-cell foreign-body reaction, forming pilomatricoma-like nodules.[21,22] Some cases may be extremely rich in cellular components (>95%) but lack mucus or cartilage interstitium, and they are called cell-rich MTS.[23] There are rare cases of MTS invading small blood vessels, but there is no recurrence or metastasis during follow-up for many years.[24] The cases of the present study agreed with these histological features.

Epithelial cells of MTS can result in hyalinization. Glass-like cells can be observed in about 40% MTS, characterized as oval shape, deeply stained glass-like or glass-like cytoplasm, and deviation of nuclei, which are known as plasmacytoid cells because they are similar to plasma cells. The literature reported that these cells have myoepithelial properties, so they should be called as "plasmacytoid myoepithelial cells."[25] These cells are still at the pluripotent stage and the direction is hard to determine; therefore, they usually have 2 patterns of expression on immunohistochemistry. In this study, clear plasmacytoid cells were found in 6 cases. Immunohistochemistry of these cases showed positive CK and Vimentin, suggesting that they were similar to myoepithelial cells, while different in the degree of differentiation. MTS interstitium can differentiate toward a variety of directions, such as mucus-like, fibroblasts, fibrocartilage-like, chondroma-like and even bone-like components, which often mixed,[26] as observed in the present study.

Immunohistochemistry revealed that inner epithelium of the gland duct mainly expressed CK, EMA, and CEA, while the outer epithelium mainly expressed CK, Vimentin, S-100, GFAP, P63, and SMA, as supported by a previous study.[27] Expression rates of desmin and actin were low in the outer epithelium of gland duct and epithelial nests, suggesting that these cells were not yet mature to support myoepithelial differentiation. Taken together, the results suggest that immunohistochemistry of MTS lacks specificity and that correct diagnosis should be made based on H&E staining. At present, most of the studies on the immunohistochemistry of MTS aimed at its occurrence, development, and prognosis. Indeed, studies have demonstrated that expressions of Bcl-2 and antigens of proliferating nuclei are correlated with the occurrence of MTS.[28] Survivin, TGF-α, and PCNA are involved in the occurrence, development, and growth of MTS,[29] while PLAG1 is overexpressed in MTS.[30]

Furthermore, clinical manifestations of MTS lack specificity. MTS should be clinically differentiated from other tumors such as epidermal cysts, trichoepithelioma, dermatofibroma, and syringoma.[31] Pathological examination is especially important to diagnose MTS.[32] Based on the differential histological diagnosis, it should be differentiated from other benign adnexal tumors such as apocrine adenoma, pilomatricomas, clear-cell hidradenoma, and sebaceous cysts.[33] It should be noted that the microscopic morphology of MTS is very similar to pleomorphic adenoma from salivary gland, which is difficult to be identified. We have innovatively discovered that immunohistochemistry had a certain prompting effect in addition to sample collection to find the existence of salivary glands. The outer epithelium and epithelial nests of the gland duct of MTS express epithelial and mesenchymal markers, and there were high expressions of S-100, GFAP, SMA, and P63, verifying that there was myoepithelial differentiation, but desmin and actin were almost negative, suggesting that the degree of differentiation was lower than that of myoepithelial cells. This is different from pleomorphic adenoma from the salivary gland, which is helpful to make a correct diagnosis of MTS.

MTS is a benign lesion, which can be cured by surgical resection alone without possibility of local recurrence. Nevertheless, the literature reports the existence of malignant MTS.[12] Microscopic manifestations of malignant MTS are heteromorphic enlargement of cells, increase in nuclear fission, infiltrative growth of the margin, satellite lesions, and tumor necrosis.[12,34] There are also reports that rare malignant MTS exist in the occipital regions, which involves the dura.[35] Metastasis of tumor can occur in lymph nodes, lung, and bone,[36] and even the central nervous

Table 4

Immunohistochemistry of interstitial component for the 21 cases of mixed tumor of the skin.

	CK	CK5/6	CK8	EMA	CEA	Vim	S-100	GFAP	Des	Actin	SMA	P63	Ki-67
Mucus-like interstitium	0	0	0	0	0	21	0	0	0	0	0	0	0%
Fibrous interstitium	0	0	0	0	0	21	0	0	0	0	0	0	0%
Cartilage-like interstitium	1	1	0	0	0	5	3	1	0	0	0	0	1%

system.[37] Thus, we recommended that follow-up should be performed after complete resection of malignant MTS.[38,39] Recurrence rarely occurs for malignant MTS after resection, but Mohs surgery should be performed to resect malignant MTS.[40,41] Recently, 1 case was reported to having developed recurrence and was diagnosed with malignant MTS 20 years after benign MTS.[42] All of the 21 cases in this study were benign. There are 7 patients who are still being followed up, without recurrence.

The present study is not without limitations. The sample size was small and from a single center. Because of the retrospective nature of the study, some data were not available in the charts. Finally, we cannot exclude the possibility that some MTS were received differential diagnoses and could not be identified from our database. Additional studies are necessary to determine the characteristics of MTS.

5. Conclusion

MTS is a rare benign tumor. Pathological diagnosis is particularly important because the clinical symptoms of MTS lack specificity.

Author contributions

Data curation: Minyan Xu.
Formal analysis: Minyan Xu.
Methodology: Tian Xia.
Writing – original draft: Huiying Wan.

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