Clinical and pathological study on mixed tumors of the skin

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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 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.

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]

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

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

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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

| Gender (male/female) | 14:7 |
|----------------------|------|
| Age, y               | 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      | 2–120|
| Range                | 2–120|
| Average              | 17.6 |
| Median               | 10   |
| Size, mm             | 5–20 |
| Range                | 5–20 |
| Average              | 14   |
| Median               | 12   |

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.
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 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.

### 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.
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. The literature reports that the incidence of MTS accounts for 0.01% to 0.098% of primary skin tumors and maybe even less. MTS usually occurs in middle-aged men, predominantly on the head and neck. Clinical features of MTS are a single subcutaneous nodule with slow growth and clear boundary. The nodules are medium hard or hard in texture, which is considered to be related to their interstitial component. Diameters of the masses are mostly

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

Histological manifestations of MTS are various, but they mainly manifest as epithelial components embedded in a mucus-like, cartilage-like, or fibrous matrix. 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.

Some cases have hair matrix differentiation, cosinophilic ghost cells, and giant-cell foreign-body reaction, forming pilomatricoma-like nodules. Some cases may be extremely rich in cellular components (>95%) but lack mucus or cartilage interstitium, and they are called cell-rich MTS. There are rare cases of MTS invading small blood vessels, but there is no recurrence or metastasis during follow-up for many years. The cases of the present study agreed with these histological features.

Epithelial cells of MTS can result in hyalinization. Glass-like matrix 1 1 0 0 0 5 3 1 0 0 0 0 1%
Fibrous interstitium 0 0 0 0 0 21 0 0 0 0 0 0 0%
Mucus-like interstitium 0 0 0 0 0 21 0 0 0 0 0 0 0%

Table 3

|                  | 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     | 21  | 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%    |

Table 4

|                  | 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 have developed recurrence and was diagnosed with malignant MTS 20 years after benign MTS. [42]

All 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.
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