

• Clinical Research •

Metastatic alveolar soft tissue sarcoma of the central nervous system: a clinicopathological analysis of four cases

Zhi-Hui Wang,¹ Huai-Yin Shi² and Zhan-Bo Wang²

¹Department of Pathology, Linyi Oncology Hospital, Linyi, Shandong, 276000, P. R. China; ²Department of Pathology, Chinese PLA General Hospital, Beijing, 100853, P. R. China

[Abstract] Background and Objective: Metastatic alveolar soft tissue sarcoma (ASTS) of the central nervous system is rare and is easy to be misdiagnosed as other primary tumors of central nervous system. This study was to analyze the clinical and pathological features of four patients with ASTS of the central nervous system and to clarify their differential diagnosis as well as prognosis. **Methods:** HE slices and clinical data of the four cases were reviewed and immunohistochemical staining was performed. Antibodies included Vimentin, Myosin, Myoglobin, S-100, Actin, Desmin, CgA, Syn, NSE, and CK. **Results:** All four patients had a skin nodule of the extremities removed previously. Clinical symptoms included headache and sight blurring. The metastatic lesions were located in the posterior cranial fossa, closely associated with the meninges. The tumor cells had clear or eosinophilic cytoplasm and prominent nucleoli, arranged in alveolar structures, which were surrounded by delicate blood sinuses. The immunohistochemical staining results showed that the positive stainings of Actin, Desmin and S-100 were in 2 cases; the weakly positive stainings of NSE and Vimentin were in 1 case; the positive staining of PAS was in all four cases. The follow-up data showed that one case died during one year after surgery, two cases died during three years. The fourth case had half year after operation and had been alive without tumour. **Conclusion:** ASTS of the central nervous system was, mostly metastatic and should be differentiated from other CNS tumors such as meningioma, melanocytic tumor, rhabdomyosarcoma and paraganglioma. Metastatic ASTS of the central nervous system has poor prognosis and the five-year survival rate was low.

Key words: brain neoplasm/secondary cases, alveolar soft part sarcoma, pathology

Alveolar soft tissue sarcoma (ASTS) is a rare tumor of soft tissues and accounts for 0.5%–1.0% of all soft tissue tumors.¹ For many years, the origin of ASTS remains controversial. Even though most scholars currently incline to the perspective of muscular origin, it still requires further concrete evidence to support this theory. ASTS is usually located in deep part of muscular tissues of four limbs and has long course of history. References reported that the course of disease could last from three months to nine years, with an average of 28.5 months. Primary intracranial ASTS is even rarer and most are due to metastasis from ASTS of soft tissues. There are only few case reports in literature.¹ We analyzed the clinicopathologic characteristics of four cases of intracranial metastatic ASTS,

investigated its diagnostic and differential features.

Materials and Methods

Samples

The four specimens of intracranial metastatic ASTS were from the patients who received surgical operation or consultation in the Tumor Hospital of Linqing City and Chinese PLA General Hospital since 1990. Of the 4 patients, three were men and one was woman, with age of 30–41 years. All pathologic slides and clinical data were reviewed; typical paraffin blocks were selected for immunohistochemical analysis.

Immunohistochemical analysis

Antibodies for actin, Vimentin, S100, Desmin, CgA, Syn, NSE, and CK were purchased from the Maxim Biological Reagents Company in Fuzhou and the Beijing Zhongshan Biological Reagents Company. SP immunohistochemical analysis was performed according to the instructions. Specific primary antibodies were diluted to ratio of 1:50. TBS took place of specific primary antibodies to serve as negative control; slides of skeletal muscle as the positive control of Actin; slides of

Correspondence to: Zhi-Hui Wang; Tel: +86-539-3690518; Email: young0831@sina.com

This paper was translated into English from its original publication in Chinese by Beijing Xinglin Medtrans Center and Wei Liu on 2009-09-30.

The original Chinese version of this paper is published in *Chinese Journal of Cancer* 28(11); <http://www.cjcsysu.cn/cn/article.asp?id=15834>.

Submitted: 2009-03-06; Revised: 2009-08-07

smooth muscle as the positive controls of Vimentin and Desmin; slides of neural fiber as the positive control of S100; slides of adrenal tissue as the positive control of CgA; slides of pancreatic tissue as the positive controls of Syn and NSE; slides of epithelium as the positive control of CK. All positive cells had their cytoplasm stained. Ten representative viewing fields under high magnification were selected to count 200 stained positive cells. A slide with the proportion of positive cells of no less than 25% would be considered as positive.

Clinical data

All patients complained of intermittent headache and two had hypopsia. MRI and CT examinations revealed occupying lesion in the posterior cranial fossa, where more specifically, two were at the left posterior cranial fossa and two were at the right posterior cranial fossa, which were closely related to meninges. Surrounding tissues were not affected and did not show sign of edema and occupying lesion. During operation, it was observed that tumors had abundant blood supply, with ambiguous boundary, and were located outside the cerebral parenchyma and near the meninges. By tracing back the history, two patients had epidermal nodules at the lower extremities in three and five years ago, which were surgically removed and there was no record of pathologic diagnosis of these nodules; the other two

patients had surgical resection of epidermal nodules at the upper arm in two and three years ago, where one was diagnosed as ASTS and another was diagnosed as alveolar rhabdomyosarcoma. No recurrence of primary lesions in the extremities occurred at the time of surgical resection of intracranial metastatic tumors. No metastasis in other organs, such as the liver and lungs, was observed. After operation, two patients received four courses of chemotherapy. The patients were followed up by phone. All four patients had complete data of follow-up.

Results

Pathologic observation

Gross observation revealed that tumors had clear boundaries. The maximal size for tumors was 5 cm × 4.5 cm × 3 cm and the minimal size was 3 cm × 3 cm × 2.5 cm. The section of tumor was in gray white. Signs of hemorrhage and necrosis were seen. Microscopic observation revealed that tumor cells were arranged as alveolar or ovarian shape of different sizes, which were surrounded by abundant capillaries or blood sinuses (Fig. 1A). Some ovarian-shaped tumors were solid and were composed of many cells (Fig. 1B). Tumor cells were relatively large and were

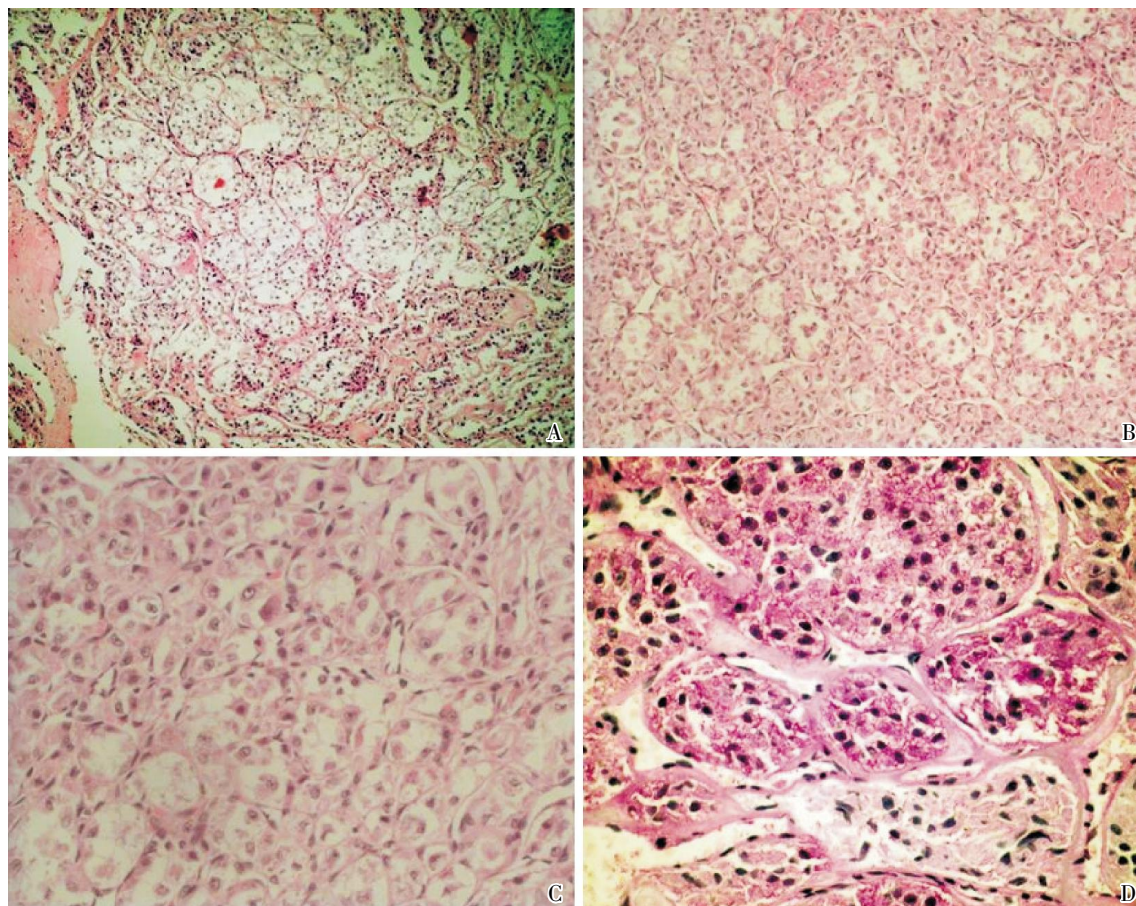


Figure 1 HE staining and PAS staining of alveolar soft tissue sarcoma

A, tumor cells arrange in alveolar pattern, surrounded with rich sinusoidal vessels (HE ×100). B, some tumor cells arrange in solid pattern, no lumen is present in these alveoli (HE ×100). C, the cytoplasm is rich, clear or eosinophilic with vesicular nuclei and prominent nucleoli (HE ×200). D, PAS staining is positive in the tumor cells (×200).

in polygonal or spherical shape. Most cells had clear boundary. Abundant cytoplasm, which was either clear or filled with acidophilic granules, was usually observed; nuclei were either round or oval in shape; chromatin was grany with clear nucleoli, and with few signs of mitosis (Fig. 1C). Reviewing the HE slides of primary nodules in the extremities of two patients, typical alveolar arrangement was seen, with abundant and clear cytoplasm as well as clear nucleoli in some cells. Morphologically, it was similar to the morphology of intracranial tumor.

Immunohistochemical and specific staining results

Two tumors expressed Actin, Desmin, and S100, while one had weak positive expression of NSE and Vimentin (Fig. 2). All tumors did not express Myoglobin, Myosin, Muscle, CK, Syn, and CgA. With specific staining, PAS was detected in all tumors (Fig. 1D).

Results of follow-up

Of the four patients, one died of intracranial recurrence and lung metastasis within one year after operation; two died of

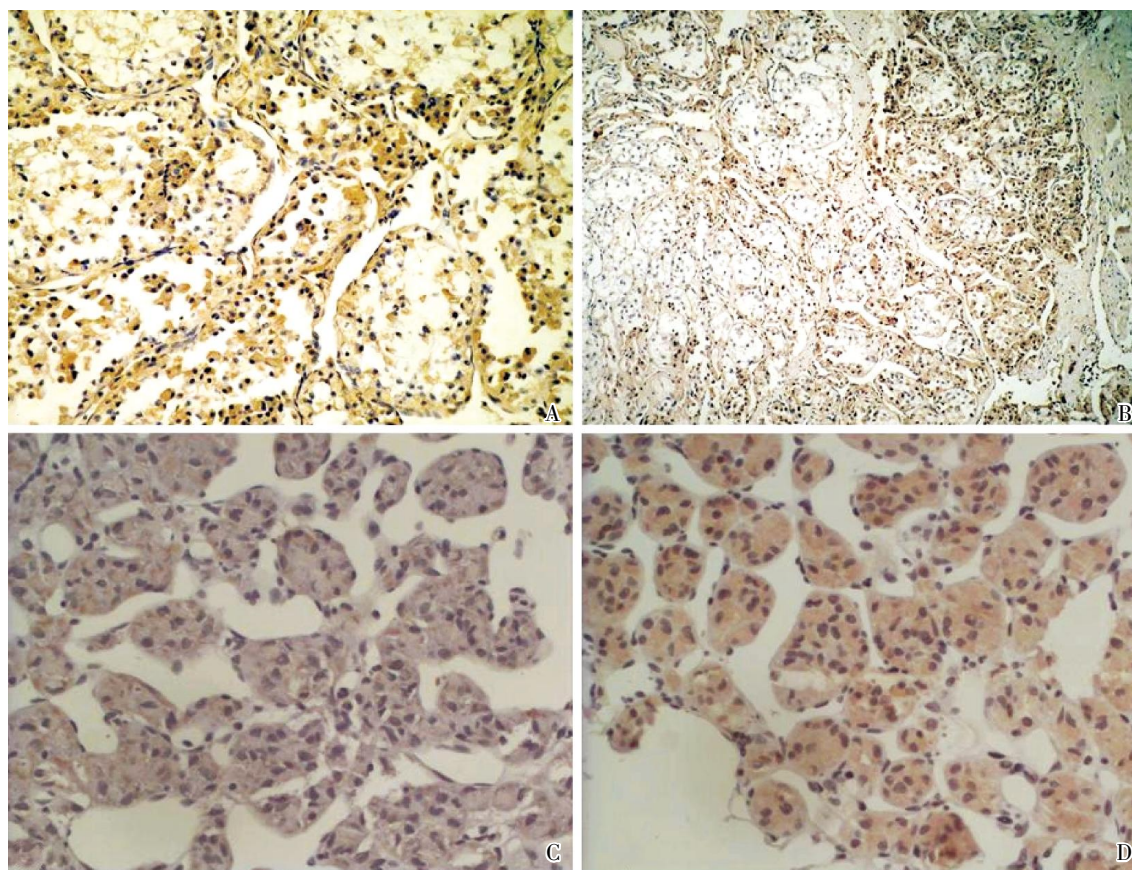


Figure 2 Immunohistochemical staining of alveolar soft tissue sarcoma

A, the tumor cells are SMA positive (SP $\times 100$); B, Desmin are positive in the tumor cells (SP $\times 100$); C, NSE is weakly positive in the tumor cells in one case (SP $\times 200$); D, S-100 is positively expressed in the tumor cells (SP $\times 200$).

intracranial recurrence at 27 and 30 months after operation, respectively; one survived for more than half a year after operation, without recurrence.

Discussion

ASTS is a rare tumor of soft tissues and takes up 0.5%–1.0% of all soft tissue tumors.¹ ASTS is mostly observed in young adults and the peak onset age was 15–35 years. Most patients are men. It is usually located in soft tissues of the extremities, especially in the lower extremities. For children, the head and neck are the mostly involved sites, specifically the orbit and tongue. Tumors in children are usually small and this is

possibly due to early discovery at the sites described above. Except for the extremities, ASTS can develop in other rare sites such as the retroperitoneal space,^{2,3} with slow growth. The longest course of disease before operation could be up to 20 years. Because of lack of pain sensation and obvious dysfunction, it is likely to be overlooked. In some cases, ASTS was identified only when the symptoms of lung and brain metastasis appeared. Generally, it is believed that ASTS in some organs such as the lungs and brain is mostly relocated from soft tissues. Its pathologic diagnostic criteria were as follows: 1) The tumor presents presents as lobules with incomplete envelop and clear boundary. Its section is gray white or grayish and it is solid like flesh of fish. Signs of hemorrhage and necrosis are

commonly seen. 2) Microscopic observation shows specific alveolar or ovarian structure, and organ-like structure formed by network of sinus-like blood vessels. Blood vessels at local blood vessel-abundant areas are dilated as spongy hemangioma-like structure. Few have tumor cells arranged in cords or flakes, with ambiguous blood vessel lumens. This type of ASTS is commonly seen in infants and usually yields good prognosis. 3) Tumor cells are large with clear boundary. Their sizes and shapes are rather uniform, even though some smaller or giant tumor cells can occasionally show up. Tumor cells have abundant cytoplasm with red fine granules and needle-like red crystals, and are PAS-positive in cytoplasm (continues to be positive even after treatment against digestion by amylase). Argyrophilic staining, mucicarmine staining, and alcian blue staining are all negative. 4) Nuclei are round, oval, or irregular. Chromatin is in fine granules and lightly stained, with clear nucleoli. There is no definite pattern in mitosis. In large tumors with obvious hemorrhage and necrosis, there is an increase in mitosis. Few tumor cells have double or multiple nuclei with deep staining and obvious heterogeneity. 5) Immunohistochemical analysis showed that no CK, EMA, NF, GFAP, FVIII_{Ag}, alpha-AT, and 5-HT can be detected in ASTS cells. References reported that muscular markers of SMA, Desmin, Myoglobin, Z-protein, and Myosin could be detected.⁴ Zhang et al.⁵ reported that Actin, Myoglobin, Myosin, and Desmin were detected in 33 of 135 cases of ASTS. Rosai et al.⁶ also detected MyoD1 protein in cytoplasm of tumor cells. MyoD1, a nuclear phosphorus protein, regulates differentiation toward myogenic cells. Recently, it was reported that ASTS cells could express S100 protein and NSE.^{4,7}

Under electronic microscope, there are diamond-, rod-, and needle-like crystals of different sizes, as well as scattered secretory granules in high electronic density in cytoplasm. In 1971, Fisher and Reidbord, based on discovery of membrane-bounded crystals in nematode rhabdomyosarcoma and myoma, proposed that ASTS might have muscular origin. Immunohistochemical staining showed expression of Desmin, SMA, HHF-35, Myosin, and Myoglobin, as well as similar cytoplasmic crystals in spindle fibers of normal human muscles. It further supports the theory of skeletal muscle differentiation for ASTS.

Because of characteristic alveolar structure in ASTS, it should be differentiated from other tumors with alveolar structure.⁸ Intracranial metastatic ASTS mostly occurs in the meninges, especially in the posterior cranial fossa. Therefore, it should also be differentiated from primary meningeal tumors. Primary diseases to be differentiated include the follows: 1) Paraganglioma. It can develop in the meninges and presents organ-like structure with abundant sinuses. Therefore, it is difficult to be differentiated from ASTS. In paraganglioma, chromatin is generally slim with the change of so-called "pepper salt" in the nuclei of neural endocrine tumor cells. Nucleoli are generally ambiguous. In addition, the alveolar changes in paraganglioma are not as apparent as in ASTS. Cytoplasm presents as acidophilic granules and hyaline degeneration is unobvious in paraganglioma. Immunohistochemical staining shows that the neural endocrine marker is positive in

paraganglioma, while negative in ASTS. This is helpful for differentiation of the two diseases. 2) Malignant granuloma. Although rare, there are still some reports of malignant granuloma in the meninges. Granuloma has abundant cytoplasm with acidophilic granules, as well as unobvious alveolar structure, blood sinuses, and clear cytoplasm, which makes it easier to be differentiated from typical ASTS. When ASTS mainly manifests large areas of solid acidophiles, it becomes difficult to be differentiated from granuloma and may require more sampling for typical areas. 3) Alveolar rhabdomyosarcoma. It is rarely observed in the cranial cavity, but its structure is very similar to alveolar rhabdomyosarcoma of soft tissues and has alveolar arrangement. The differentiation is based on the existence of interstitial fibrous tissues between alveoli instead of sinuses acidophilic cytoplasm, deviated nuclei and unobvious nucleoli in alveolar rhabdomyosarcoma, and negative PAS staining in rhabdomyosarcoma. 4) Cancers with abundant blood sinuses. Intracranial metastases of some tumors with abundant blood sinuses, such as hepatic carcinoma, adrenal carcinoma and hepatoid adenocarcinoma, need to be differentiated from primary or metastatic ASTS because they all have abundant sinuses and clear cytoplasm. Cancer tissues usually present obvious heterogeneity with beam-like solid nests instead of classical alveolar structure. Necrosis and mitosis are commonly observed. More sampling will reveal typical regions. Immunohistochemical analysis is helpful for differentiation.

Intracranial ASTS is rare and most are from metastasis of ASTS in soft tissues.^{9,10} In this study, all cases were metastatic and these patients had history of surgical removal of soft tissue nodules. Sometimes, it takes long time for metastasis to occur and there is even report of as long as 30 years for intracranial metastasis.¹¹ We analyzed the clinicopathologic characteristics of these four cases of metastatic ASTS and found that all intracranial metastatic ASTS migrated to the meninges, especially in the posterior cranial fossa, none migrated to the cerebral parenchyma. Its histological morphology was similar to the ASTS in soft tissues, but it sometimes lacked obvious alveolar structures and arranged solidly. However, close observation further revealed a trend to form alveoli as well as abundant cytoplasm and obvious nucleoli. Intracranial metastatic ASTS needs to be differentiated from other meningeal tumors, such as meningioma, paraganglioma, malignant melanoma and rhabdomyosarcoma. The prognosis of intracranial metastatic ASTS is poor and the 5-year survival rate is rather low. In this study, three of four patients died within five years after operation, one survived for more than half a year without recurrence after operation, but the survival still requires further observation.

References

- [1] Zarrin-Khameh N, Kaye KS. Alveolar soft part sarcoma [J]. Arch Pathol Lab Med, 2007, 131(3):488-491.
- [2] Ishikawa M, Ishizuka O, Nakayama T, et al. Alveolar soft-part sarcoma of the retroperitoneum[J]. Int J Urol, 2006, 13(10):1355-1357.
- [3] Kim YD, Lee CH, Lee MK, et al. Primary alveolar soft part sarcoma of the lung [J]. J Korean Med Sci, 2007, 22(2):369-372.
- [4] Khanna P, Paidas CN, Gilbert-Barness E. Alveolar soft part sarcoma: clinical, histopathological, molecular, and ultrastructural aspects [J].

- Fetal Pediatr Pathol, 2008,27(1):31-40.
- [5] Zhang RY. Alveolar soft part sarcoma: clinical pathology analysis and ultra-structure observation [J]. Chin J Oncol,1984,6 (2):116 -119. [in Chinese]
- [6] Rosai J, Dias P, Parham DM, et al. MyoD1 protein expression in alveolar soft part sarcoma as confirmatory evidence of its skeletal muscle nature [J]. Am J Surg Pathol, 1991,15(10):974-981.
- [7] Hu PA, Zhou ZR, Peng WJ, et al. Radiological features and clinicopathological findings of alveolar soft part sarcomas [J].CHINA ONCOLOGY,2009,19(1):12-16.
- [8] Folpe AL, Deyrup AT. Alveolar soft-part sarcoma; a review and update [J]. J Clin Pathol, 2006,59(11):1127-1132.
- [9] Akiyama Y, Baba T, Ibayashi Y, et al. Alveolar soft part sarcoma in brain with cardiac metastasis: a case report [J]. Int J Cardiol, 2007,114(3): 93-95.
- [10] Sujit Kumar GS, Chacko G, Chacko AG, et al. Alveolar soft-part sarcoma presenting with multiple intracranial metastases[J]. Neurol India, 2004,52(2):257-258.
- [11] Lillehei KO, Kleinschmidt-DeMasters B, Mitchell DH, et al. Alveolar soft part sarcoma: an unusually long interval between presentation and brain metastasis [J]. Hum Pathol, 1993,24(9):1030-1034.