Original Article

Comparison study of clinicopathological features of cellular schwannoma between retroperitoneum and other sites

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Background: Cellular schwannoma (CS) is a relatively rare neural tumor with few reports. This study aimed to compare the clinicopathological characteristics of CS in the retroperitoneum and other sites by analyzing the hematoxylin-eosin (HE) staining and immunohistochemical (IHC) staining results, to provide some help for pathological diagnosis.

Methods: A total of 79 CS cases from the Department of Pathology, Peking University International Hospital were collected, and the diagnosis was based on the 5th WHO classification of soft tissue tumors. The staining results of HE and IHC were judged and analyzed according to the instructions. The *t*-tests, Chi-square test and Fisher's exact probability test were used for statistical analysis.

Results: Compared with other sites, the volume of retroperitoneal CS tumors were larger (t=4.265, P=0.001) and more likely to recur (χ^2=4.223, P=0.04). Nerve sheath structures were rare around the tumors (χ^2=60.096, P=0.000). Immunohistochemically, there was a difference in the expression of glial fibrillary acidic protein (GFAP), Cytokeratin (CK), and myelin basic protein (MBP) between the two groups (χ^2=54.290, P=0.000; χ^2=4.879, P=0.027; χ^2=31.792, P=0.000). But there was no difference in expression between the two groups in the other indexes.

Conclusions: It founded that Retroperitoneal CS was often positive for GFAP and CK, suggesting it originated from unmyelinated Schwann cells. CS in other sites, the expression of GFAP and CK was often negative, indicating they derived from myelinated Schwann cells. The expression of MBP in the peripheral nerve sheath structure of CS can be used to determine whether the tumor originates from myelinated or unmyelinated Schwann cells. These findings may provide a reference for revealing pathogenesis, diagnosis and evaluating prognosis of CS.

Keywords: Retroperitoneal; cellular schwannomas (CS); immunohistochemistry

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Introduction

Cellular schwannoma (CS) is a rare nerve tumor originating from Schwann cells, accounting for 2.8–5.2% of schwannoma (1,2); this tumor often occurs in the posterior mediastinum, pelvis, retroperitoneum, followed by head and neck, trunk, limbs, spinal canal and intracranial (3-6); in clinical practice, we found that retroperitoneal CS is not only large in size, easy to recur, but also has the phenomenon of invading surrounding tissues, but no reports of malignant change have been found (7,8); the CS in other parts is generally small in size and rarely invades the surrounding tissues, but cases of recurrence and

malignant transformation are found (9-11); the reasons for their different clinicopathological characteristics have not been reported.

Studies have found that (7,12) the majority of nerves in the retroperitoneum are unmyelinated and often express glial fibrillary acidic protein (GFAP), whereas nerves in other sites (central and peripheral) are mostly myelinated and there are obvious morphological and functional differences between unmyelinated and myelinated Schwann cells (13). Therefore, we speculate that the differences in clinicopathological characteristics of CS between retroperitoneum and other sites may originate from different Schwann cells; there are fewer studies on retroperitoneal CS, and a comparison of the differences in clinicopathological characteristics between CS in the retroperitoneum and other sites is rare.

This paper collected 79 cases of CS, including 45 cases in the retroperitoneum and 34 cases in other sites (such as the head and neck, trunk, limbs, vertebral canal, intracranial, etc.). It observed and summarized their clinicopathological characteristics. It also compared the differences between the two groups, in order to reveal the pathogenesis of different parts of CS. More importantly, it provided reference for pathological diagnosis and evaluation of prognosis. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4979/rc).

Highlight box

Key findings

- This study found the pathological difference between CS in the retroperitoneum and other sites.

What is known and what is new?

- Studies have found that the majority of nerves in the retroperitoneum are unmyelinated and often express GFAP, whereas nerves in other sites (central and peripheral) are mostly myelinated and there are obvious morphological and functional differences between unmyelinated and myelinated Schwann cells.
- Retroperitoneal CS originated from unmyelinated Schwann cells. CS in other sites derived from myelinated Schwann cells.

What is the implication, and what should change now?

- CS in the retroperitoneum and other sites comes from different Schwann cells, leading a new understanding of CS, makes pathological diagnosis, treatment and prognosis evaluation more accurate.

Methods

Clinical data

79 cases were diagnosed as CSs from December 2014 to August 2022 were collected from the Department of Pathology, Peking University International Hospital. According to the different distribution positions of myelinated and unmyelinated nerve fibers, they were divided into two groups: retroperitoneal CS and CS in other sites (the central nervous system and peripheral nervous system are usually myelinated nerve fibers, while retroperitoneal nerve fibers are usually unmyelinated nerve fibers). The clinical information and imaging data of patients were recorded using the electronic medical record system and reviewed by two chief physicians. There were 45 cases of retroperitoneal and 34 cases of other sites, including the head and neck, trunk, extremities, intraspinal, intracranial, etc. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking University International Hospital [No. 2018-062 (BMR)] and informed consent was taken from all the patients.

Immunohistochemical detection method

79 samples were fixed with 10% neutral formalin, then routinely dehydrated, paraffin embedded and cutted into 3 μm thickness sections at last. The sections were stained with hematoxylin-eosin (HE) and immunohistochemical (IHC) respectively. EnVision two-step method was used for immunohistochemical staining. The primary antibodies used were CK, CD34, GFAP, SOX-10, S-100, P53, P16, Ki-67, Nerve Fiber (NF), type IV collagen, P75, Desmin, H3 lysine 27 trimethylation (H3K27me3) and myelin basic protein (MBP). The operation was carried out according to the antibody description, and the positive and negative controls were set up.

Statistical analysis

SPSS version 26.0 (IBM Corporation, Armonk, New York, USA) statistical software was used for statistical description and analysis of data. The mean age and size of tumor between the two groups were compared using an unpaired two-sided Student's *t*-test. The clinical pathological indicators and each immunohistochemical

Table 1 Comparison of the clinicopathological features of cellular schwannomas in the retroperitoneum and other sites

Clinicopathological indicators	Retroperitoneal	Other sites	χ^2	P value
Sex, n (%)				
Male	20 (44.4)	13 (38.2)		
Female	25 (55.6)	21 (61.8)	0.307	0.580
Recrudescence, n (%)				
Yes	8 (17.8)	1 (2.9)		
No	37 (82.2)	33 (97.1)	4.223	0.04
Malignant transformation, n (%)				
Yes	0 (0)	1 (2.9)		
No	45 (100.0)	33 (97.1)		0.430
Invade surrounding tissues, n (%)				
Yes	3 (6.7)	0 (0)		
No	42 (93.3)	34 (100.0)	0.885	0.347
Nerve sheath structure of tumor periphery, n (%)				
Yes	1 (2.2)	30 (88.2)		
No	44 (97.8)	4 (11.8)	60.096	0.000

indicators between the two groups were compared by using Chi-square test and Fisher's exact probability test. P<0.05 showed that the difference was statistically significant.

Results

General clinical features

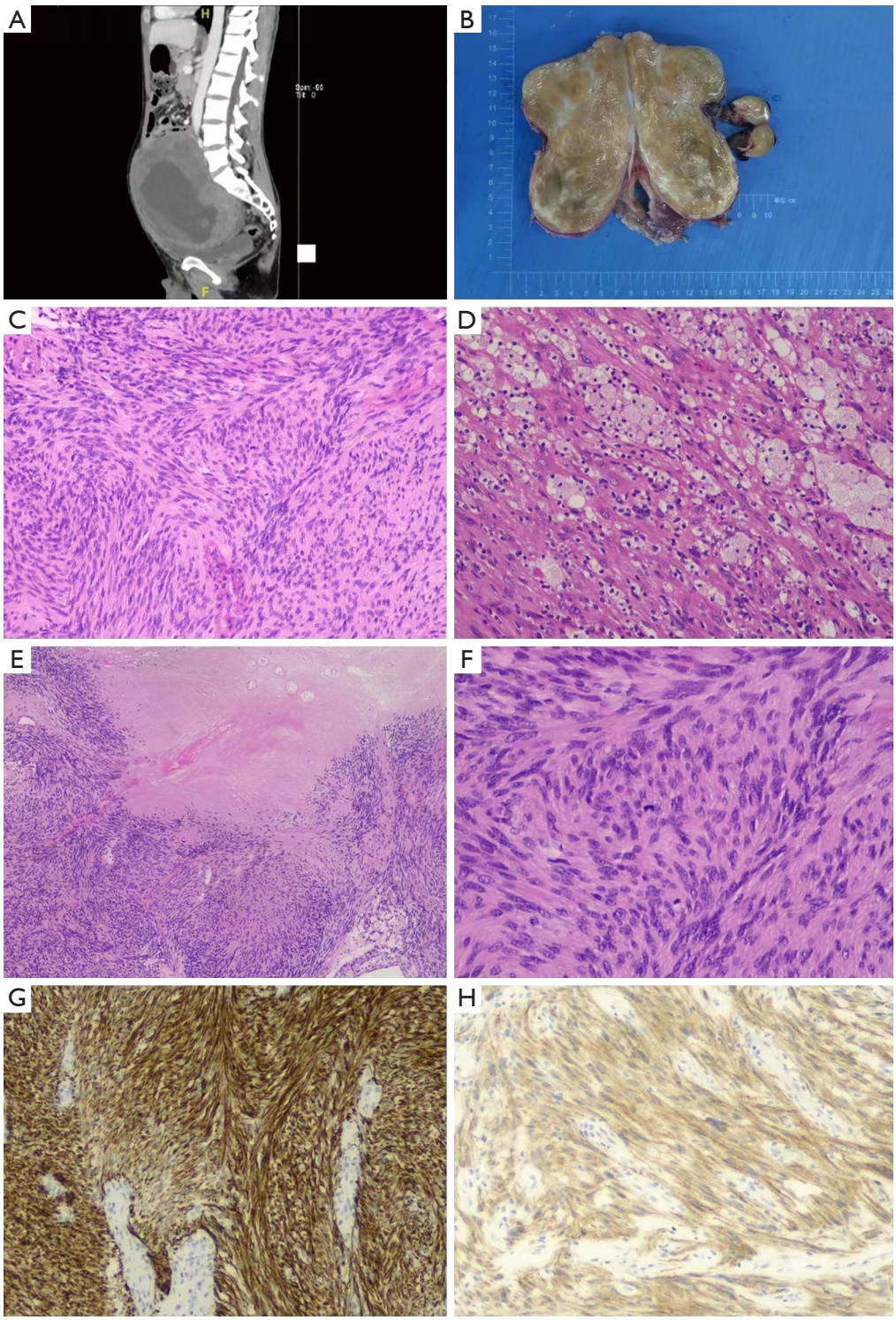
Among the 45 cases of retroperitoneal CS, there were 20 males and 25 females, with a male-to-female ratio of 1:1.25, and a median age of 43 years (range, 20–70 years); Among the 34 CS cases at other sites, there were 13 males and 21 females, with a male-to-female ratio of 1:1.61 and a median age of 40.7 years (range, 20–70 years). There were no significant differences in gender and median age between the groups (*Table 1*).

Eight cases of retroperitoneal CS recurred after surgery, and no malignant transformation was found. The recurrence time interval was 3–18 years. Also, one case in the other sites (located intracranially) recurred locally after CS surgery and underwent malignant transformation, with a time interval of 3 years. In terms of recurrence, the difference between the two groups was statistically significant, while that in terms of malignant transformation was not (*Table 1*).

Morphological characteristics

The 79 cases of CS were similar to classical schwannomas, with clear boundaries and a tumor diameter of 1–20 cm. The retroperitoneal tumors had a diameter of 2.5–20 cm, with an average of 9.05 cm (*Figure 1A*), and there were often multiple tumors. Meanwhile, the tumors in other sites had a diameter of 1–8 cm, with an average of 3.18 cm, and there was usually a single tumor. The difference between retroperitoneal tumors and those in other sites was statistically significant.

Most of the tumors had a complete or partial capsule, and the section was gray white and gray yellow (*Figure 1B*). Bleeding and cystic changes could be seen in some cases. Microscopically, the tumor cells were densely arranged in a fascicular or interlaced arrangement, and were light to moderate heterotypic (*Figure 1C*). The foci of foam cell accumulation were observed (*Figure 1D*), and thick-walled vessels with hyalinization as well as perivascular and subcapsular lymphocytic infiltration could also be seen. In some cases, vortex-like structures were observed, and nerve fiber bundles and nerve sheath structures were seen in the periphery of the tumor in some CS cases in the other sites, however, nerve fiber bundles were found in the periphery of the retroperitoneal tumors, while nerve sheath structures



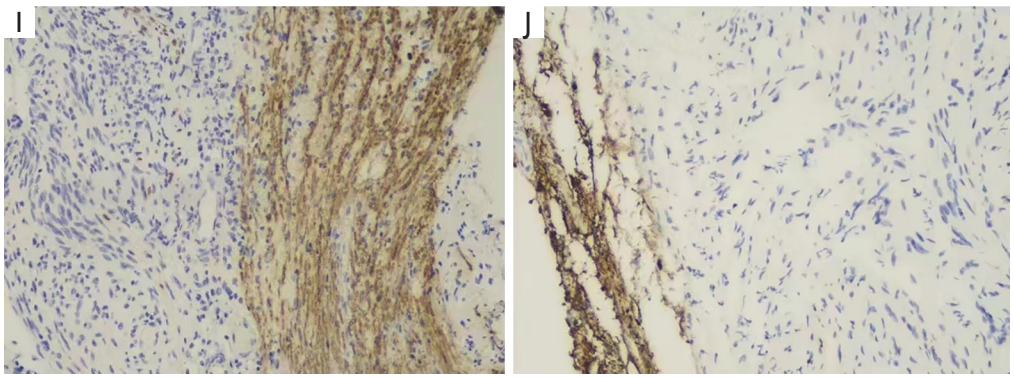


Figure 1 Picture of CS imaging, gross, HE staining and IHC staining. Enhanced CT showing retroperitoneal cellular schwannomas (A); the tumor has a capsule, and the section is grayish white and grayish yellow (B); cells are arranged in bundles or interlaces, with slight heteromorphism (HE ×100) (C); the aggregation of foam cells (HE ×100) (D); obvious necrosis (HE ×40) (E); the mitotic image (HE ×200) (F); Diffuse strong positive GFAP in the retroperitoneum (IHC En Vision ×100) (G); CK diffuse weak medium positive (IHC En Vision ×100) (H); MBP shows the nerve sheath structure at the periphery of the CS tumor in the other sites (IHC En Vision ×100) (I); NF shows the nerve fibers around the tumor (IHC En Vision ×100) (J). CS, cellular schwannoma; HE, hematoxylin eosin; IHC, immunohistochemical; CT, computed tomography; GFAP, glial fibrillary acidic protein; CK, cytokeratin; MBP, myelin basic protein; NF, nerve fiber.

were rarely seen, and the difference was statistically significant (*Table 1*).

There was one case (intracranial) of malignant transformation in the other sites, and most of the areas were CS, with obvious focal cell atypia and necrosis (*Figure 1E*). The difference of malignant transformation was not statistically significant (*Table 1*). Moreover, there were three cases of retroperitoneal CS involving the surrounding bowel, mesentery, and fatty renal capsule, and the difference of invade surrounding tissues was not statistically significant (*Table 1*). The mitotic figures of all cases showed 0–4/1 high-power field (HPF) (*Figure 1F*), while there was one case (intracranial) of focal malignant transformation in the other sites. The mitotic figures of different regions were quite different; those in the CS area were 0–4/HPF, and those in the focal malignant area were 3–6/HPF, with focal necrosis. Ossification and calcification were observed in a few cases.

Immunophenotyping (Table 2)

GFAP was diffusely medium strong positive in all 45 cases (45/45) of retroperitoneal CS (*Figure 1G*), while only seven cases (7/34) of CS in the other sites were weak medium positive in the focal area or around the tumor, and the difference was statistically significant (P=0.000). CK was diffusely weak moderate positive in 23 cases (23/45) of retroperitoneal CS (*Figure 1H*), while only 9 cases (9/34) of CS in the other sites were focal or partially weak positive, and the difference was statistically significant (P=0.027). The MBP immunohistochemical staining results showed that the residual nerve sheath structure around the tumor was positive (*Figure 1I*). One case (1/45) of retroperitoneal CS was positive, and the positive nerve sheath structure was distant from the tumor, while 20 cases (20/34) of CS in the other sites were positive, and the difference was statistically significant (P=0.000). Moreover, NF showed residual nerve fibers around the tumor (*Figure 1J*); 5 cases (5/45) of retroperitoneal CS were positive and 7 cases (7/34) in the other sites were positive, with no statistical difference. Other immunohistochemical markers (CD34, p16, Ki-67, type IV collagen, p75, desmin, and H3K27me3) showed no significant difference between the two groups. Sox-10 and S-100 showed focal or diffuse weak strong positive expression in both groups of cases. P53 was wild type.

Discussion

Schwann cells are the most common type of peripheral nerves, which can be further divided into myelinated Schwann cells, unmyelinated Schwann cells, perisynaptic Schwann cells, and peripheral satellite cells (14-16). Increasing evidence (12,13,17) has shown that these glial cells not only play a key role in immune regulation and

Table 2 Comparison of the immunophenotype of cellular schwannomas in retroperitoneum and other sites

Immunohistochemical markers	Retroperitoneal	Other sites	χ^2	P value
CK, n (%)				
+	23 (51.1)	9 (26.5)		
–	22 (48.9)	25 (73.5)	4.879	0.027
CD34, n (%)				
+	15 (33.3)	17 (50.0)		
–	30 (66.7)	17 (50.0)	2.232	0.135
GFAP, n (%)				
+	45 (100.0)	7 (20.6)		
–	0 (0.0)	27 (79.4)	54.290	0.000
P16, n (%)				
+	45 (100.0)	33 (97.1)		
–	0 (0.0)	1 (2.9)		0.430
Ki-67, n (%)				
≥10%	12 (26.7)	13 (38.2)		
<10%	33 (73.3)	21 (61.8)	1.198	0.274
NF at the periphery of the tumor, n (%)				
+	5 (11.1)	7 (20.6)		
–	40 (88.9)	27 (79.4)	1.350	0.245
Type IV collagen, n (%)				
+	29 (64.4)	21 (61.8)		
–	16 (35.6)	13 (38.2)	0.060	0.807
P75, n (%)				
+	25 (55.6)	25 (73.5)		
–	20 (44.4)	9 (26.5)	2.693	0.101
Desmin, n (%)				
+	42 (93.3)	27 (79.4)		
–	3 (6.7)	7 (20.6)	2.253	0.133
H3K27Me3, n (%)				
+	15 (33.3)	12 (35.3)		
–	30 (66.7)	22 (64.7)	0.033	0.856
MBP at the periphery of the tumor, n (%)				
+	1 (2.2)	20 (58.8)		
–	44 (97.8)	14 (41.2)	31.792	0.000

CK, cytokeratin; GFAP, glial fibrillary acidic protein; NF, nerve fiber; H3K27Me3, H3 lysine 27 trimethylation; MBP, myelin basic protein.

maintenance of normal nervous system functions but also play an important role in nerve injury and disease. They also exert an important function in repair and pain but their functions and morphology are significantly different (13), leading to tumors generated by Schwann cells, which may have different clinicopathological characteristics. It has been reported in the literature (7,12) that unmyelinated nerve fibers are more common in the retroperitoneum, and myelinated nerve fibers are more common in the peripheral nerves. Based on the above, this study analyzed and compared 79 cases of Schwann CSs that occurred in the retroperitoneum and other sites.

Clinicopathological features

There were no significant differences in terms of gender and median age between the retroperitoneal CS and CS in the other sites. In this study and clinical work, we found that tumor recurrence and invasion of surrounding tissues were more common in retroperitoneal CS; however, no reports of malignant transformation have been identified (7,8). Meanwhile, there are reports of recurrence and malignant transformation of CS in the other sites. In this study, one case of intracranial CS had malignant transformation, which is consistent with the literature reports (9-11). The difference in recurrence between the two groups was statistically significant, while that in terms of malignant transformation was not. The recurrence difference may be explained by the fact that retroperitoneal tumors are not easily removed, or that CS derived from unmyelinated Schwann cells is more prone to recurrence, which needs to be further confirmed. The lack of a difference in terms of malignant transformation may be attributable to the small number of cases, which could not represent the spectrum of the disease.

This study also found that the typical nerve sheath structure was rarely seen around the retroperitoneal CS tumor, and only one case exhibited a nerve sheath structure but it was far from the tumor, which may be analyzed as a residual myelinated nerve in the retroperitoneum. In the other CS sites, the nerve sheath structure was often seen around the tumor, and the difference of nerve sheath structure of tumor periphery was statistically significant, but there were residual nerve fibers around the two tumor groups. This may be because retroperitoneal CS is derived from Schwann cells of unmyelinated nerve fibers, so the formation of the neural sheath structure is not typical, however, further confirmation is needed.

Immunohistochemical features

In addition to the partial clinicopathological differences between retroperitoneal CS and CS in other locations, there are also some immunophenotypical differences between these two groups. GFAP is a glial fibrillary acidic protein and marker for glial activation, and its gene maps to band 1 of region 2 of the long arm of chromosome 17. Glial cells often become diffusely positive. A study (7) reported that not all Schwann cells express GFAP; it is only often expressed by unmyelinated Schwann cells. The present study found that the positive rate of GFAP expression in retroperitoneal CS (100%) was significantly higher than that in other parts of CS (20%) ($P<0.05$), while Fanburg-Smith *et al.* (18) reported that the positive rate of GFAP in retroperitoneal schwannomas was 90% (104/115). This is because the authors did not distinguish between classic and CSs. The low GFAP expression rates in CS in other locations may be attributable to the fact that most of the peripheral nerves are myelinated nerve fibers, and the morphology and function of Schwann cells differ from those of unmyelinated nerve fibers, which further supports that retroperitoneal CS is derived from unmyelinated Schwann cells.

CK expression was also significantly different between the two groups of cases ($P<0.05$), suggesting that the Schwann cell functions at the two sites were different. But other reports said the different may be cross-reactions between GFAP and CK (18). However, further research is needed to confirm this.

MBP is a myelin basic protein. It is a single-chain flexible polypeptide (about 18.5 kd), which is located in the dense myelin sheath and nucleus pulposus. It is often used as a marker for oligodendrocytes and Schwann cells. In this study, it was found that few Schwann cells exhibited positive MBP expression around the retroperitoneal CS. Only one case of positive expression around the tumor was found; however, this was not adjacent to the tumor or located in the tumor envelope but was located in the surrounding fibrous adipose tissue (more than one low power field of view (×40) distance, speculated to be Schwann cells of residual myelinated nerves). Meanwhile, Schwann cells with positive expression of MBP could be seen in the other sites of CS, often located under, within, or adjacent to the inner capsule of the tumor, which suggests that MBP may not

be expressed or is less expressed in unmyelinated Schwann cells. Thus, it is inferred that there are differences between the functions of unmyelinated and myelinated Schwann cells, suggesting that there are differences in the tumor origin and clinicopathological characteristics between retroperitoneal CS and CS in other sites.

P75 is a neurotrophic factor receptor and a member of the tumor necrosis factor (TNF) receptor family. It is mainly expressed in Schwann cells and neurons as well as some other non-neural cell types and plays a role in regulating neuronal growth, migration, differentiation, and cell death during the development of the central and peripheral nervous systems. It has been documented that p75 is highly expressed in both unmyelinated and myelinated Schwann cells (19), and the expression rate in malignant peripheral schwannoma (80%) is significantly higher than that in CS (31%) (20). The present study found that there was no significant difference in the expression of p75 in CS in the retroperitoneum and other sites, indicating that p75 only suggested that the tumor was derived from Schwann cells, and had little effect in distinguishing between unmyelinated and myelinated Schwann cells. Also, the positive expression rate of p75 in CS was high (64%), which is inconsistent with previous literature reports (20) and needs to be confirmed by further research.

There was no significant difference in Ki-67 expression between the two groups. However, we found that the proportion of Ki-67 ≤10% in retroperitoneal CS was higher than that in other sites. Although this result was not statistically significant, it further suggested that other sites of CS might have higher value-added activity and a greater probability of malignant transformation, which is consistent with the literature (9-11).

There was no significant difference in the positive rate of NF around the tumor between the two groups. On the one hand, this suggested that a small number of nerve fibers remained around the tumor, and both groups were closely related to nerve fibers, and on the other, it highlights that there was no difference in the expression of NF between unmyelinated and myelinated nerve fibers.

H3K27me3 refers to the trimethylation of lysine at position 27 of histone H3, which participates in the regulation of gene expression, gene imprinting, and X-chromosome inactivation, regulates embryonic development as well as cell proliferation and differentiation, and is closely related to cell aging and tumorigenesis. In malignant peripheral nerve sheath tumors, the expression of H3K27me3 is often reduced or absent (21). A study had found that this reduced or absent expression is often indicative of a poor prognosis or malignant transformation tendency (22). In this study, we found that the expression of H3K27me3 was reduced or lost in both groups; however, there was no significant difference between the two groups, suggesting that H3K27me3 did not affect the occurrence, development, and prognosis of CS in the two groups.

CD34 is often reticular positive in neurofibromas, but local reticular expression is often absent in neurofibromas with malignant transformation (23), and its expression is often absent or scattered cytoplasmic positivity is seen in malignant peripheral nerve sheath tumors (24). In this study, reticular positivity was observed in the peripheral nerve fibers of tumors in both groups, but no reticular positive expression was found in the tumors themselves. A small number of positives were scattered or focal positives. CD34 was also scattered positive in one case of intracranial malignant transformation. These findings suggested that CD34 has no obvious significance in differentiating the malignancy of CS in different sites.

P16 is often expressed positively in neurofibromas and schwannomas (23,25), and is often absent in malignant peripheral nerve sheath tumors (26). However, no loss of expression was found in CS in this study, and there was no obvious difference in its expression between the two groups, suggesting that p16 has no obvious effect in differentiating and speculating on the relationship with malignant peripheral nerve sheath tumors, and cannot be used as a predictor of CS malignancy.

In terms of collagen IV and desmin, there was no statistical significance between the two groups, suggesting that these immunohistochemical indicators also exhibit no obvious advantage for identifying the source, occurrence, development, and prognosis of the two groups. Sox-10 and S-100 were expressed consistently in both groups of cases, at least one marker was expressed, and p53 was wild type.

Conclusions

In this study, the clinical manifestations, gross pathological characteristics, and immunohistochemistry of retroperitoneal CS and CS in other sites were compared and analyzed in detail. It founded that Retroperitoneal CS was often positive for GFAP and CK, suggesting it originated from unmyelinated Schwann cells. CS in other sites, the expression of GFAP and CK was often negative, indicating they derived from myelinated Schwann cells. The expression of MBP in the peripheral nerve sheath structure of CS

can be used to determine whether the tumor originates from myelinated or unmyelinated Schwann cells. These findings may provide a reference for revealing pathogenesis, diagnosis and evaluating prognosis of CS. However, this study also has some limitations, such as failing to analyze the differences in Schwann cell functions between the two groups from a molecular biological perspective. In summary, recognizing the clinicopathological differences between retroperitoneal CS and CS in other locations may provide a basis for the differential diagnosis and prognostic evaluation in clinicopathological work.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4979/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4979/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4979/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking University International Hospital [No. 2018-062 (BMR)] and informed consent was taken from all the patients.

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