Hybrid schwannoma/perineurioma of the spinal nerve: multifocal occurrence, and recurrence as an intraneural perineurioma

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Short title

Spinal hybrid schwannoma/perineurioma

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Abstract

A 63-year-old Japanese man complained of lower back pain and numbness and was diagnosed as intradural tumors at the T11/12 and L1 level. The thoracic tumor originated from the posterior nerve root, and the lumbar tumor originated from the cauda equina. Five months after surgical resection, the patient developed recurrent tumor consisting of enlargement of multiple caudal nerves. Pathologically, the primary tumors showed a nodular and lobular pattern, including spindle cells in a fascicular, whorl and storiform pattern, with variable cellularity, nuclear palisading and frequent small onion bulb structures. Mild pleomorphism was present, and there were four mitoses per 10 high power fields. Many cells showed immunoreactivity for S-100 and Sox10. There were also claudin-1-positive spindle cells, but no epithelial membrane antigen (EMA)-positive cells. The cells in onion bulb structures were positive for claudin-1 and glucose transporter 1 (GLUT-1). These findings led a diagnosis of hybrid schwannoma/perineurioma. The features of high cellularity, pleomorphism and a Ki-67 index over 10% suggested low-malignant nature. The recurrent tumor also showed high proliferative activity, as reflected by mitotic figures and a Ki-67 index of 20%. This is the first case of spinal nerve hybrid schwannoma/perineurioma with low malignant potential and peculiar intraneural perineurioma component.

Key words

hybrid, schwannoma, perineurioma, spinal nerve, malignant, recurrent

Introduction

Benign peripheral nerve sheath tumors can be classified as schwannomas, neurofibromas or perineuriomas, while malignant tumors are collectively classified as malignant peripheral nerve sheath tumors (MPNST).[1] Schwannoma consists of Schwann cells that stain positively for S-100 protein and Sox 10 and exhibit specific histologic feature of nuclear palisading in an Antoni A or Antoni B pattern.[2] Perineuriomas consist of perineurial cells that stain positively for epithelial membrane antigen (EMA), claudin-1 and glucose transporter 1 (GLUT-1),[3,4] and can be further subclassified into soft tissue perineuriomas and intraneural perineuriomas.[1] Neurofibromas consist of Schwann cells, perineurial cells and fibroblasts, defining neurofibromatosis type 1.[1,5]

In addition to these benign tumors, a “hybrid tumor” has been described that has mixed features of different histologic subtypes. Previous studies have reported that these tumors have components of schwannoma and neurofibroma,[6] schwannoma and perineurioma,[7,8] neurofibroma and perineurioma[9] or a mixture of all three types.[10] Mixed peripheral neural tumors have not yet been extensively studied.

The present report describes the case of a patient with spinal nerve tumors having mixed histologic features of schwannoma and perineurioma. In contrast to previous reports, the tumor from the present case showed high proliferative activity, recurred after surgical excision, and had features of intraneural perineurioma. This report raises important issues regarding the origin of peripheral nerve sheath tumors.

Clinical summary

A 63-year-old Japanese man, with no clinical sign of neurofibromatosis, presented to our Department of Orthopedics with a chief complaint of pain and numbness in the lower back extending to the buttocks and legs for several months. Magnetic resonance imaging (MRI) revealed gadolinium-enhanced intradural tumors at T11/12 and L1 with clear margins (Fig. 1). Surgical resection was planned.

At the thoracic level, the 1.5 × 0.9-cm tumor originated from the posterior nerve root (Fig. 2 A&C), and at the lumbar level, a 2.2 × 1.7-cm tumor was connected to the cauda equina (Fig. 2 B&D). Both tumors were detached and were resected en bloc. The postoperative course was uneventful and the patient’s symptoms resolved. At the operation, other caudal nerves without tumor showed no abnormalities.

However, 5 months after the operation, the patient had symptomatic recurrence, and MRI revealed

recurrent tumor in the lumbar area (Fig. 3 A). At re-operation conducted 9 months after the first operation, many caudal nerves were enlarged and filled the subdural space (Fig. 3 B). For the purposes of functional preservation, pain relief, and to confirm diagnosis, the largest tumor was excised. One month after the second operation, pain in the lumbar region, buttocks and lower leg worsened, and lower leg strength decreased. MRI revealed tumor enlargement, and radiation therapy was selected.

Pathological findings

Primary tumor

The lesions at the thoracic and lumbar levels were both nodular tumors with a lobular pattern, consisting mainly of spindle cells in a fascicular, whorl and storiform pattern. The tumor showed variable cellularity, and a myxoid nodular area was scattered in the solid proliferative area (Fig. 4 A). There were also foci showing nuclear palisading (Fig. 4 B). Frequent small onion-bulb structures, consisting of spindle and epithelioid cells, were found (Fig. 4 A,C).

The tumor cells showed mild pleomorphism. There were areas of high cellularity with a fascicular pattern and four mitoses per 10 high-power fields (Fig. 4 D). Immunohistochemically, many cells showed a positive reaction for S-100 protein (Dako, Tokyo, Japan; polyclonal, 1:4000) and for Sox10 (Santa Cruz Biotechnology, Dallas, TX, USA; goat polyclonal, 1:100, heat) (Fig. 5 A). In addition, many spindle cells showed a positive reaction against claudin-1 (Invitrogen, Camarillo, CA, USA; polyclonal, 1:100, heat) (Fig. 5 B). The S-100- and Sox10-positive cells were located in myxoid or palisading areas, and the claudin-1-positive cells were located in between the S-100- and Sox10-positive cells. There were also mixed areas of both components.

The cells in the onion-bulb structures stained positively for claudin-1 and GLUT-1 (IBL, Fujioka, Japan; polyclonal, 1:100) (Fig. 5 C), and, in the center, there were axons with neurofilament proteins (Dako, clone 2F11, 1:400, heat). The tumor cells were negative for EMA (Dako, clone E29, 1:400, heat). The labeling index of Ki-67 (Dako, clone MIB-1, 1:200, heat) varied, with some areas having an index >10% (Fig. 5 D). The area with frequent mitoses and high Ki-67 labeling index was located in the S-100 positive cell region. On the basis of these findings, the tumor was determined to be composed of Schwann cells and perineurial cells. The onion-bulb structure area was similar to intraneural perineurioma. The features of high cellularity, cell pleomorphism, and a high Ki-67 labeling index indicated a borderline or low malignant tumor.

Recurrent tumor

Examination of cross-sections of the enlarged cauda equina showed multiple small concentric structures consisting of spindle cells in an onion-bulb-like lamellar array (Fig. 6 A). There were scattered mitotic figures (Fig. 6 B), although the tumor cells lacked pleomorphism.

Immunohistochemically, the spindle cells were positive for claudin-1 (Fig. 6 C) and negative for S-100 protein. There were neurofilament-positive axons in the center of the onion-bulb concentric structures. The Ki-67 labeling index was as high as 20% in some areas (Fig. 6 D).

Considering the specific histology and the positive claudin-1 findings, the recurrent tumor was thought to be due to perineurial cell proliferation, simulating intraneural perineurioma. The high proliferative activity was consistent with a low malignant potential.

Discussion

Previous reports suggest that most representative mixed peripheral nerve sheath tumors are mixed schwannoma-perineuriomas.[7,8] Cases described by Michal featured multinodular tumors with a central reticular perineurioma component and surrounding schwannoma cells, and these tumors are found most often in the fingers of adults.[7] In the case series described by Hornick, a mixture of Schwann cells and perineurial cells was present within the same tumor[8] and these lesions occurred over a wide range of patient ages and had a predilection for formation in the limbs, head and neck, and trunk. The tumors were located at the dermis to subcutis levels and were nodular with clear margins. They consisted of spindle cells in storiform, whorl and lamellar structures. Two-thirds of the tumor cells were S-100-positive Schwann cells, and the remaining one-third were EMA- or claudin-positive perineurium cells. The tumor cells were never positive for both Schwann cell markers and perineurial markers.

The present case consisted of a mixed schwannoma/perineurioma occurring in an adult spinal nerve. The lesion primarily consisted of spindle cells, but variable histologic patterns were observed, with some showing clearly distinct areas with one of the two components and other areas consisting of a mixture of both types of cells. In addition, there were intraneural perineurioma-like components with onion-bulb structures.[1,11] Immunohistochemically, we could confirm that this tumor had proliferation of both S-100-positive Schwann cells and perineurial cells with claudin-1 and GLUT-1 positivity. Although EMA is the

representative marker for perineurial cells, it is not always detected.[1] Therefore, claudin-1 and GLUT-1 should also be used as markers when assessing the presence of perineurial cells. Indeed, in the present case, perineurial elements were deemed to be present according to the detection of claudin-1 and GLUT-1, even though EMA was absent. Based on the experimental findings, the current case met the definition of hybrid schwannoma/perineurioma. Furthermore, this is the first report to describe this type of tumor arising from the spinal nerve.

In the present case, there were two tumors (at the thoracic and lumbar level, respectively) present at the time of the patient's initial visit, and the tumor recurred several months after surgical resection. The primary tumor showed pleomorphism and atypia, and both primary and recurrent tumor showed mitoses and a high Ki-67 labeling index. These results indicate that the tumors in the present case had borderline or low malignant properties. It is difficult to determine whether two primary tumors were present or whether one tumor represented a metastatic focus of the other. From the fact that the two tumors were distant without bridging lesion, and the tumor did not show other multiple disseminations, we speculate them to be double primaries. As for the second caudal tumors, we speculate them as the direct invasion of the remnant of the primary tumor, since there had been no abnormalities in the caudal nerve at the first operation, and the recurrences occurred at the local neighboring nerves, not forming the distant metastases.

Until now, no malignant hybrid schwannoma/perineuriomas have been described.[7,8] Furthermore, except for one reported case with incomplete resection, neither recurrence nor metastasis has been described. Thus, most reported mixed schwannoma/perineuriomas are thought of as benign, but there could be cases with malignancy, similar to our case. There is a case report of MPNST associated with hybrid schwannoma/perineurioma morphology in soft tissue of thigh.[12] Although the authors concluded the tumor to be the malignant transformation of the hybrid tumor, it might have been the multi-differentiation of MPNST. However, this case could be the other end of the extreme of the spectrum of this tumor.

Another interesting finding in the present case was the presence of the onion-bulb proliferative pattern, which is a specific feature of intraneural perineurioma. Although previously described cases of hybrid tumor had onion-bulb patterns,[7,8] the present case showed both a soft tissue perineurioma pattern and an intraneural perineurioma pattern. Since the tumor cells had a predisposition for perineurial cells, it is likely that the tumor surrounded the axon in the cauda equina or spinal nerve to form the specific onion bulb pattern. That is, the tumor of the soft tissue type and the intraneural type are not distinct subtypes; rather,

the same tumor cells may show different histologic patterns according to specific backgrounds (e.g., collagen-rich soft tissue, neuron-rich nerve).

The differential diagnosis of the present case included various types of peripheral nerve sheath tumors. Although there was evident Schwann cell proliferation in the present case, specific patterns, such as the palisading pattern or Antoni A or B area, were not predominant. In addition, the perineurioma-related cells were evidently mixed in this case. These findings were useful to differentiate the present case from schwannoma. Neurofibromas show a mixture of Schwann cells, perineurial cells and fibroblast components throughout the tumor,[1,5] which is different from hybrid tumors that show areas of different histologic subtypes. As neurofibromas do not show the onion-bulb pattern, our case could be differentiated from neurofibroma. By definition, perineuriomas do not contain S-100-positive Schwann cells.[1,13]

The present case consisted of a tumor with low malignant potential and therefore should be differentiated from MPNST. In general, MPNSTs have high malignant potential, and mostly show poor histologic differentiation.[1] Therefore, tumors with a mixture of differentiated histologic patterns should not be classified as MPNST.

The histologic origin of the peripheral nerve sheath tumor remains unclear. Schwann cells are neuroectodermal cells originating from the neural crest, while perineurial cells are thought to originate from the stromal cells presenting near the nerve early in development.[14,15] The different histologic origins of these two cell types make it difficult to reconcile the origin of a tumor consisting of both cell types. It might be easier to understand if we think as follows: that the perineurial cells are also neuroectodermal in origin, and that there are common progenitor cells for both Schwann cells and perineurial cells. However, the immunohistological features, including Sox 10 expression, are largely different in these cell types, and hybrid tumors are very rare. Therefore, accumulation of additional cases is needed for further molecular and genetic study.

In summary, this is the first report to describe a case of spinal nerve hybrid schwannoma/perineurioma with low malignant potential and a peculiar finding of an intraneural perineurioma component.

This case was presented at the 102nd Annual Meeting of the Japanese Society of Pathology.

Ethics and conflict of interest

We prepared the manuscript not to be identified the patient's personal information. This case report was approved by the Institutional Review Board of Nagasaki University Hospital (Approval # 13022538).

Disclosures

None declared.

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Figure Legends

Figure 1. Magnetic resonance imaging (MRI) findings at the first operation.

There are tumors at the thoracic and lumbar vertebra levels (arrows) (A: T2-weighted image, B: gadolinium-enhanced image).

Figure 2. Intraoperative and excised tumor view (A & C: thoracic, B & D: lumbar). The tumors are encapsulated and white in color and have vessels on the surface.

Figure 3. Tumor recurrence at 8 months after the first operation.

A & B: Magnetic resonance imaging (MRI) reveals recurrent tumor at the lumbar level, similar to the location of one of the original tumors (A: T2-weighted image, B: gadolinium-enhanced image).

C: Intraoperative view shows that many caudal nerves, which seemed to be normal at the time of the first operation, are enlarged and fill the subdural space.

D: Excised enlarged nerve.

Figure 4. Pathology of the primary tumor.

A: The tumor consists of spindle cells with variable cellularity. The low cellular areas are myxoid. Small whorl formation is observed in the lower area of the photograph (hematoxylin-eosin [HE] stain, ×100).

B: Area of nuclear palisading (HE, ×200).

C: Multiple small whorl formations by epithelioid-shaped tumor cells. The stroma is rich in fibrous material (HE, ×200).

D: Focal area of atypical spindle cells in a fascicular pattern with a mitotic figure (arrow) (HE, ×250).

Figure 5. Immunohistochemical findings of the primary tumor (×200).

A: Sox10-positive Schwann cells proliferate in a fascicular pattern (upper left). On the other hand, spindle cells in the right lower area of this photograph are negative for Sox 10.

B: Claudin-1-positive cells (upper left) and -negative cells (bottom right) are present.

C: Tumor cells in whorl formations are strongly positive for glucose transporter 1 (GLUT-1).

D: High cellular area, with a Ki-67 labeling index as high as 10%.

Figure 6. Histologic findings of the recurrent tumor.

A: Whorl formation pattern is evident (HE, ×200).

B: Whorl pattern consists of concentric formation of spindle cells. Mild atypia and mitosis (arrow) are observed (HE, ×400).

C: Tumor cells in whorl pattern are positive for claudin-1 (×400).

D: The Ki-67 labeling index of the recurrent tumor is increased to 20% (×200).

Figure 1

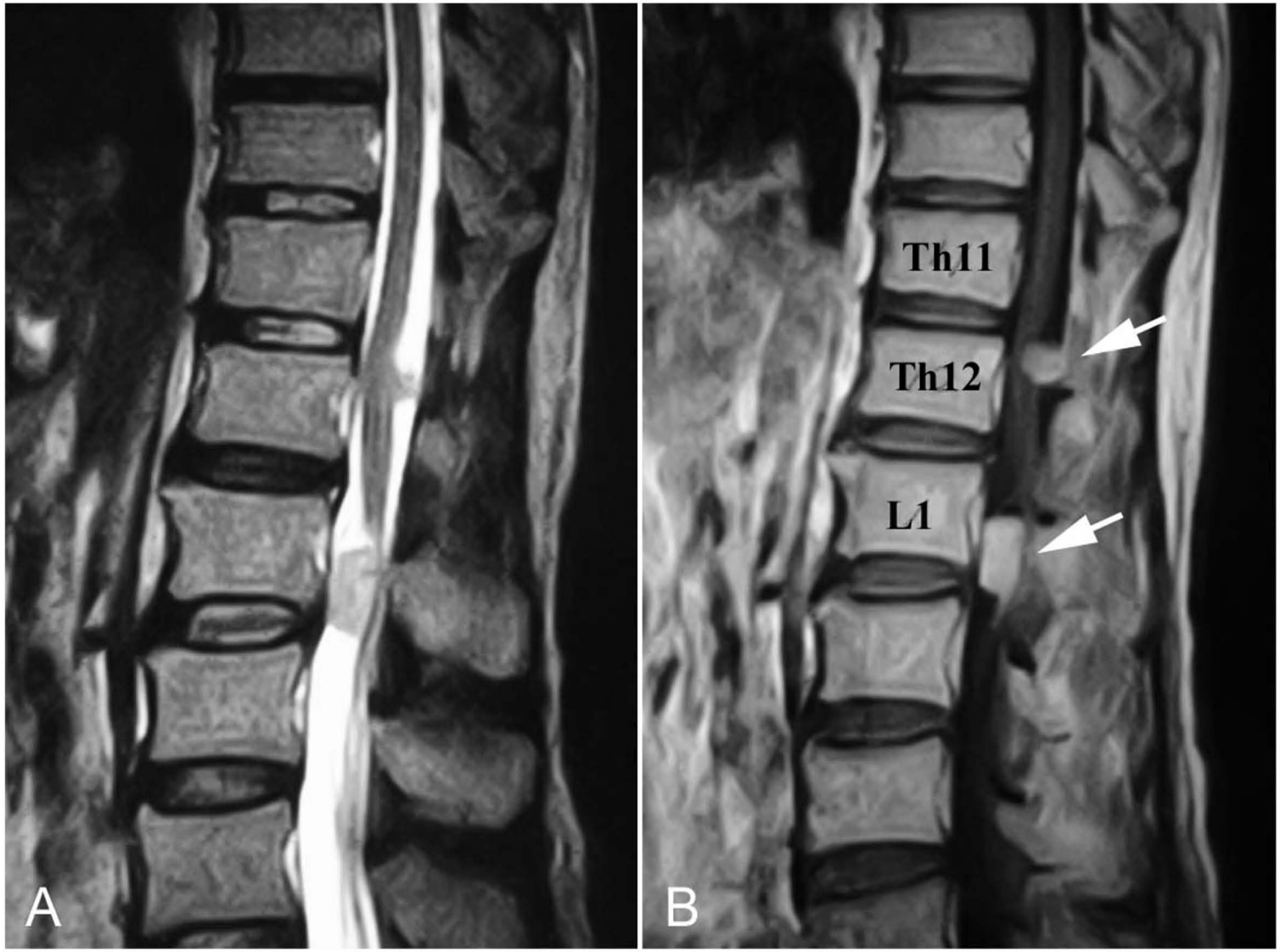
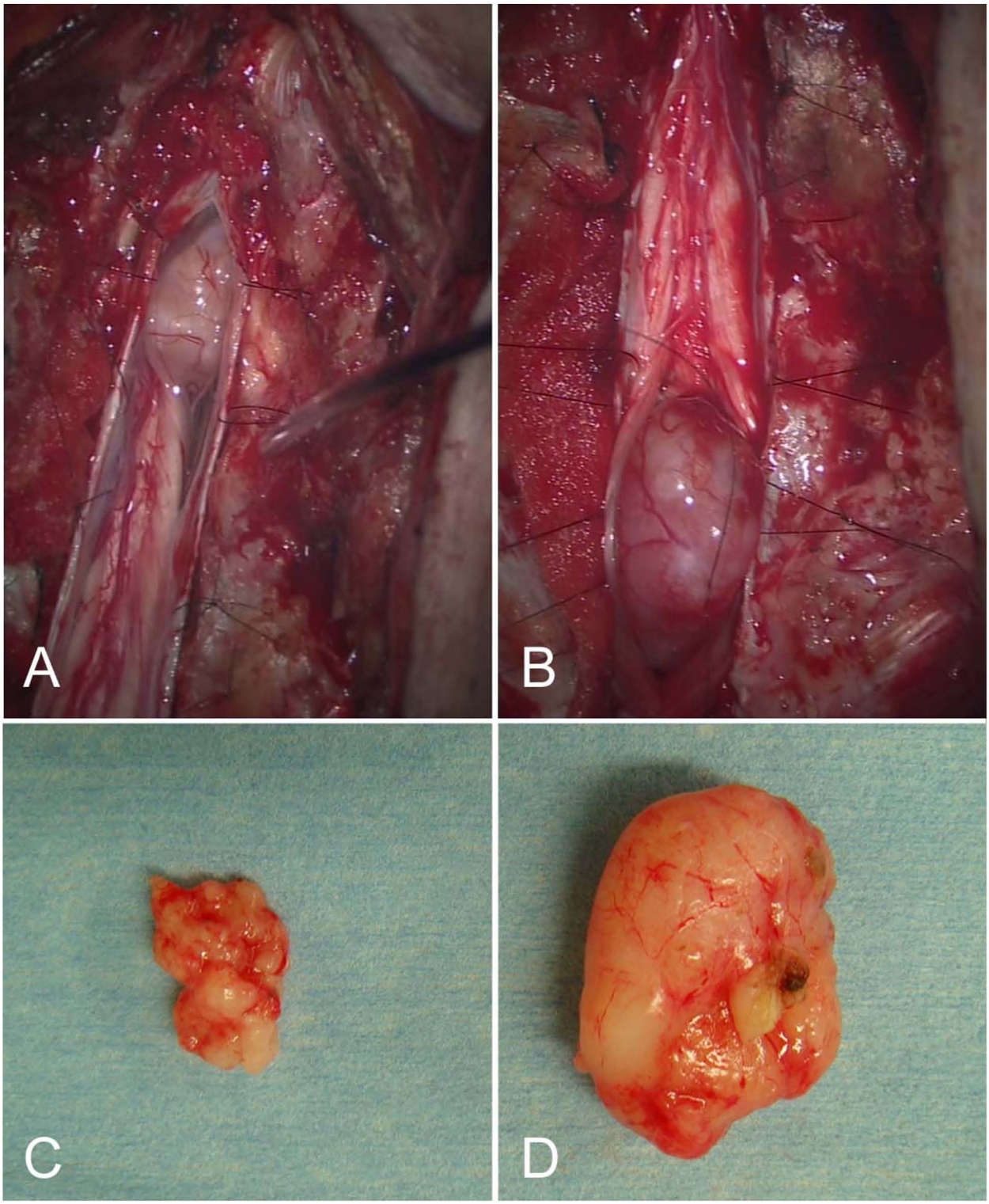


Figure 2



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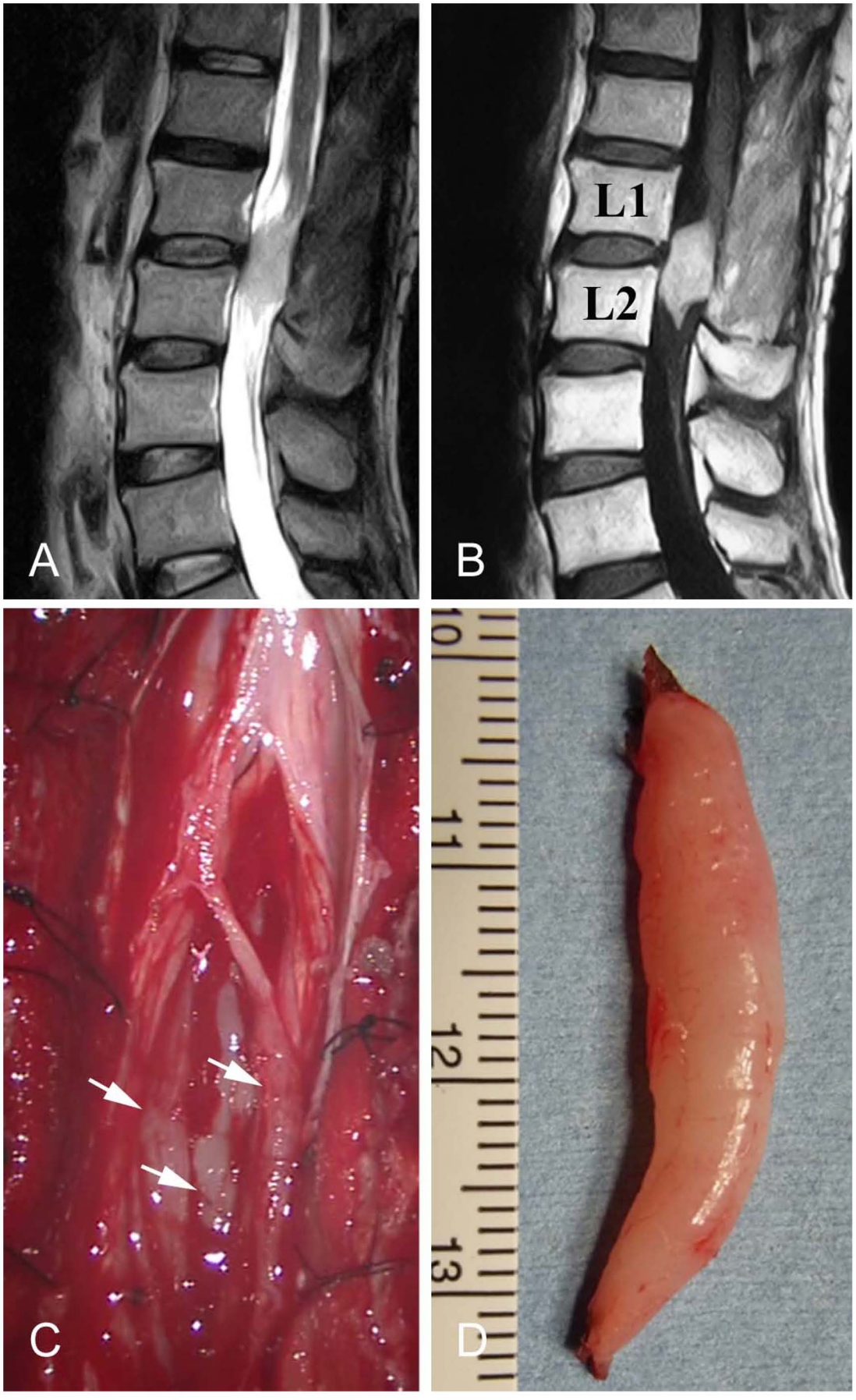

Figure 4

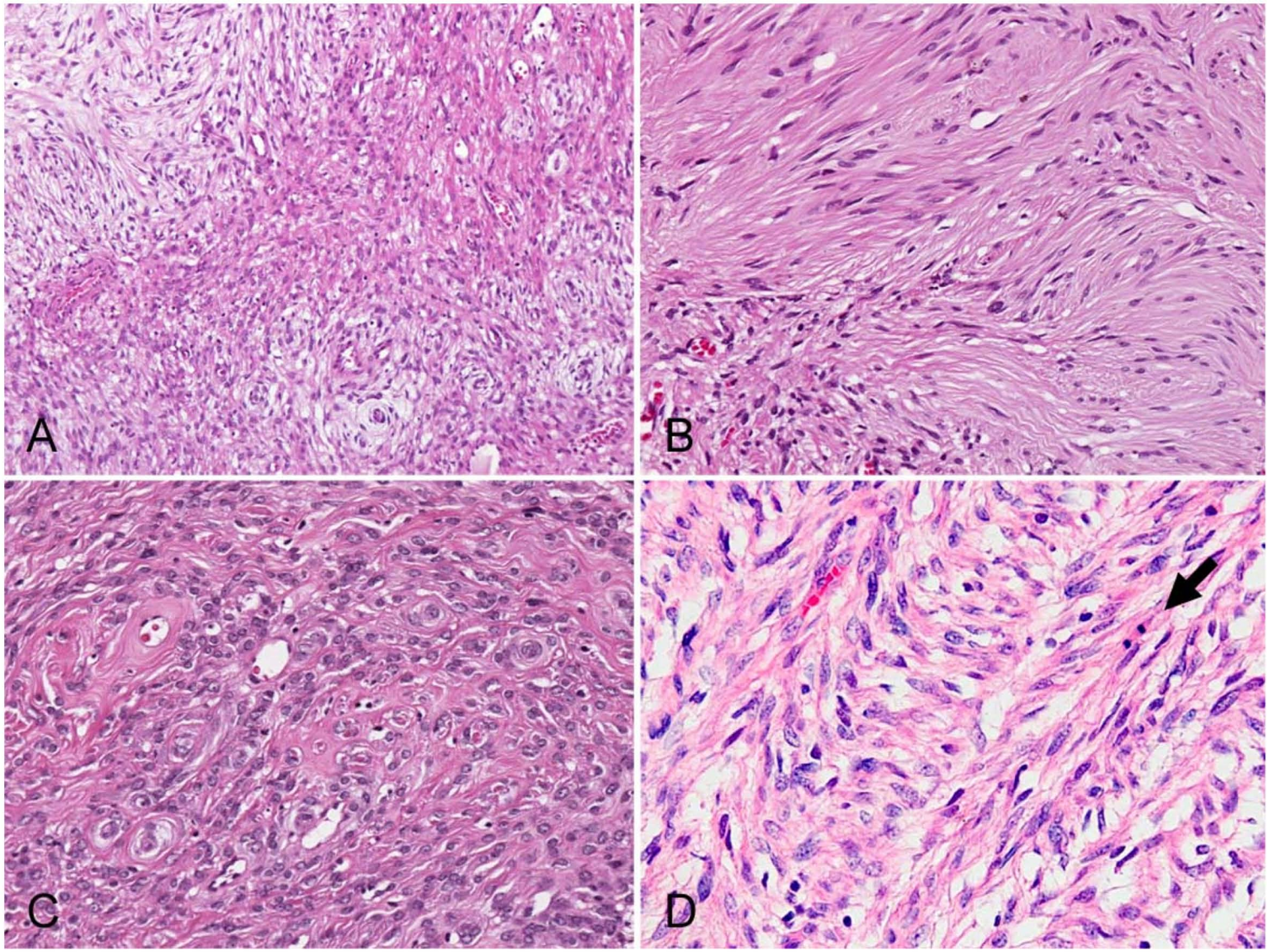

Figure 5

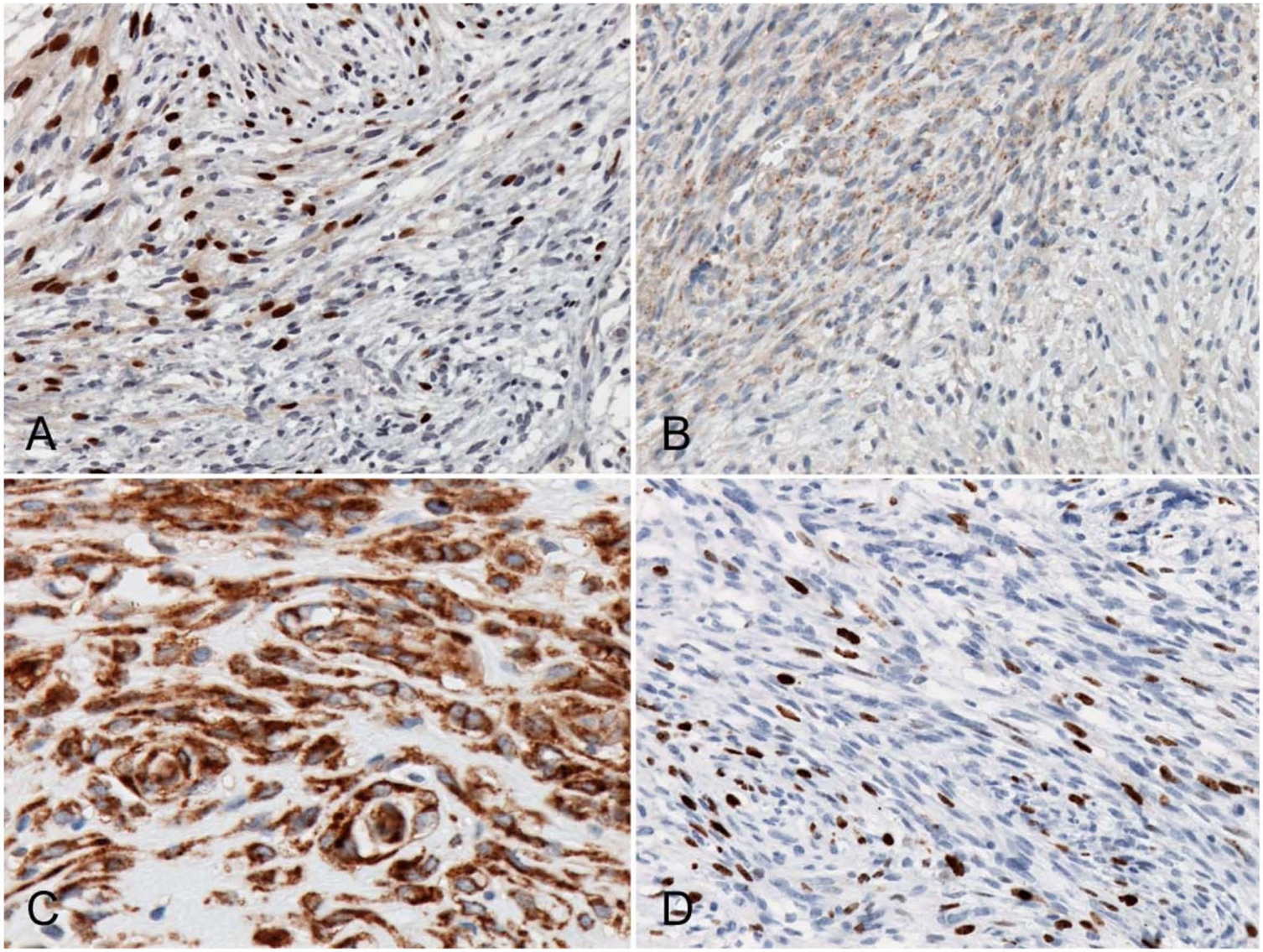

Figure 6