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Case Report

Malignant Transformation of Benign Intraosseous Schwannoma in the Cervical Spine: A Case Report with an Immunohistochemical Study

Xinsheng Peng[1], Liyan Chen[1], Hong Du[2], Yingrong Lai[3], Fobao Li[1], Xuenong Zou[1]

[1]*Department of Spinal Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

[2]*Department of Pathology, the First People's Hospital of Guangzhou City, Guangzhou, China*

[3]*Department of Pathology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Although 3% to 30% of lesions in von Recklinghausen disease undergo malignant transformation, malignant transformation of benign solitary schwannoma is extremely rare. We reported a case of recurrence and malignant transformation in a benign intraosseous schwannoma arising in the cervical spine of a 44-year-old man. The patient presented giant tumor in the C3 vertebral body with aggressive, expansile, and osteolytic destruction and relapsed 2 years after surgical resection and spinal reconstruction. Clinical data, radiologic characteristics, surgical management, histopathologic and immunohistochemical features were noted in the duration of follow-up. The local recurrence, nuclear pleomorphism, epithelioid differentiation, a small number of positive S-100 protein-staining cells, and especially the high percentage of positive cells with p53 (80%) and Ki-67 (75%) proteins support the aggressive nature of the lesion in malignant transformation of benign intraosseous schwannoma in the cervical spine. Immunohistochemistry would be useful as an ancillary technique in diagnosis. It is our practice to suggest that such case has to be carefully resected and the patient followed up.

Key words: Benign schwannoma – Malignant transformation – Intraosseous schwannoma – Immunohistochemistry

Reprint requests: Xinsheng Peng, Department of Spinal Surgery, the First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan 2rd Road, 510080 Guangzhou, Guangdong Province, China.
Tel.: +86 20 87755766 8898; Fax: +86 20 87332150; E-mail: pengxs66@tom.com

Schwannomas make up almost one-third of primary spinal neoplasms.[1] Spinal schwannomas are typically intradural-extramedullary neoplasms thought to be arisen from Schwann cells or their progenitors, which occur proportionally throughout the spinal canal.[2,3] Transdural and extradural growth is reported to occur in approximately 30% of patients.[1,3] The benign nature of spinal schwannomas is well documented in the literature.[3–5]

An intraosseous schwannoma is the infrequent occurrence and uncommon lesion. The mandible is the most common site.[6] The incidence of the intraosseous schwannomas is less than 0.2% in primary bone tumors.[7] Cases of the osseous changes in the spinal schwannomas are observed in almost one third of cases (6 of 17) where, radiographically, 1 or 2 vertebral bodies can be seen eroded with well-defined marginal sclerosis.[4] The most common imaging findings of extradural spinal schwannomas involving bone include pedicle erosion, vertebral body scalloping, and widening of the neural foramen.[8] Based on the radiologic findings, Sridhar *et al*[9] proposed a classification system of spinal schwannomas as types I to V, in which type V of spinal schwannomas was defined as a giant invasive tumor in spinal intraosseous schwannomas. In a few patients the tumor presents as an expansile vertebral body lesion in the cervical spine, as reported in the literature.[6,9–12]

Although primary malignant peripheral nerve sheath tumors (MPNSTs) of spine with or without the intraosseous involvement in association with von Recklinghausen's disease (neurofibromatosis type I) have been reported in the thoracic and lumbar spine,[12–15] malignant transformation of benign solitary schwannoma is extremely rare.[16,17] Woodruff *et al*[17] described 2 patients with such changes involving a finger and pelvis and reviewed 7 patients with malignant transformation. Malignant transformation of benign schwannoma has also been occurred in the vestibular nerve,[18] retropharyngeal space,[19] neck,[20] and intrathoracic extrapleural space[21] without an association of von Recklinghausen disease. The possibility of occult malignancy could also be associated with a previous radiation.[18,22] To our knowledge, malignant transformation of benign intraosseous schwannomas in the spine has not been reported yet.

We have managed and followed up 1 patient with a giant invasive intraosseous schwannoma in the cervical spine. This prompted us to pay special attention to the natural course of malignant transformation of an intraosseous schwannomas in the cervical spine associated with both diagnosis and treatment and to add our experience to the other scattered communications in the literature.

Materials and Methods

A 44-year-old man had a giant invasive intraosseous schwannoma in the cervical spine at the first admission and a recurrence 2 years postoperatively. Plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) were routinely performed before admission and during follow-up. MRI angiography was also done. Clinical data collection, surgical treatment, and follow-up were performed at Department of Spinal Surgery, the First Affiliated Hospital of Sun Yat-sen University.

The resected tissue fragments were fixed in 10% buffered formalin, routinely processed, and imbedded in paraffin. Hematoxylin and eosin-stained sections (4 μm) were prepared. Two independent neuropathologists (D. H. and Y.-R. L.) reviewed all tumor pathology.

Representative slides were available for immunohistochemical studies. For immunohistochemistry staining of S-100, Ki-67, and p53, the streptavidin peroxidase method was used.

The highest count of positive cells for Ki-67 and p53 in 10 high-power fields was recorded for primary and secondary specimens collected during the operation. For Ki-67 and p53 estimation, the percentage of positive nuclear staining was calculated by examining 500 tumor nuclei in the subjectively most positive areas in the sections.

The study was approved by the Institutional Ethical Board of the First Affiliated Hospital of Sun Yat-sen University and written informed consent was obtained from the patient.

Results

Clinical presentation and follow-up review

The patient presented with a 6-month history of progressive dizziness and mild weakness in the right upper limb with no sensory disturbance and tenderness in his neck. The radiographic lateral and posteroanterior cervical spine revealed the C3 vertebral collapse, loss of the right C3 pedicle and C3 to C4 disc space, enlargement of intervertebral foramen between C2 and C3, and displacement of C2 and C3 vertebrae anteriorly (Fig. 1A). CT of the cervical spine showed an expansile, osteolytic, and invasive lesion involving in the C3 vertebral body.

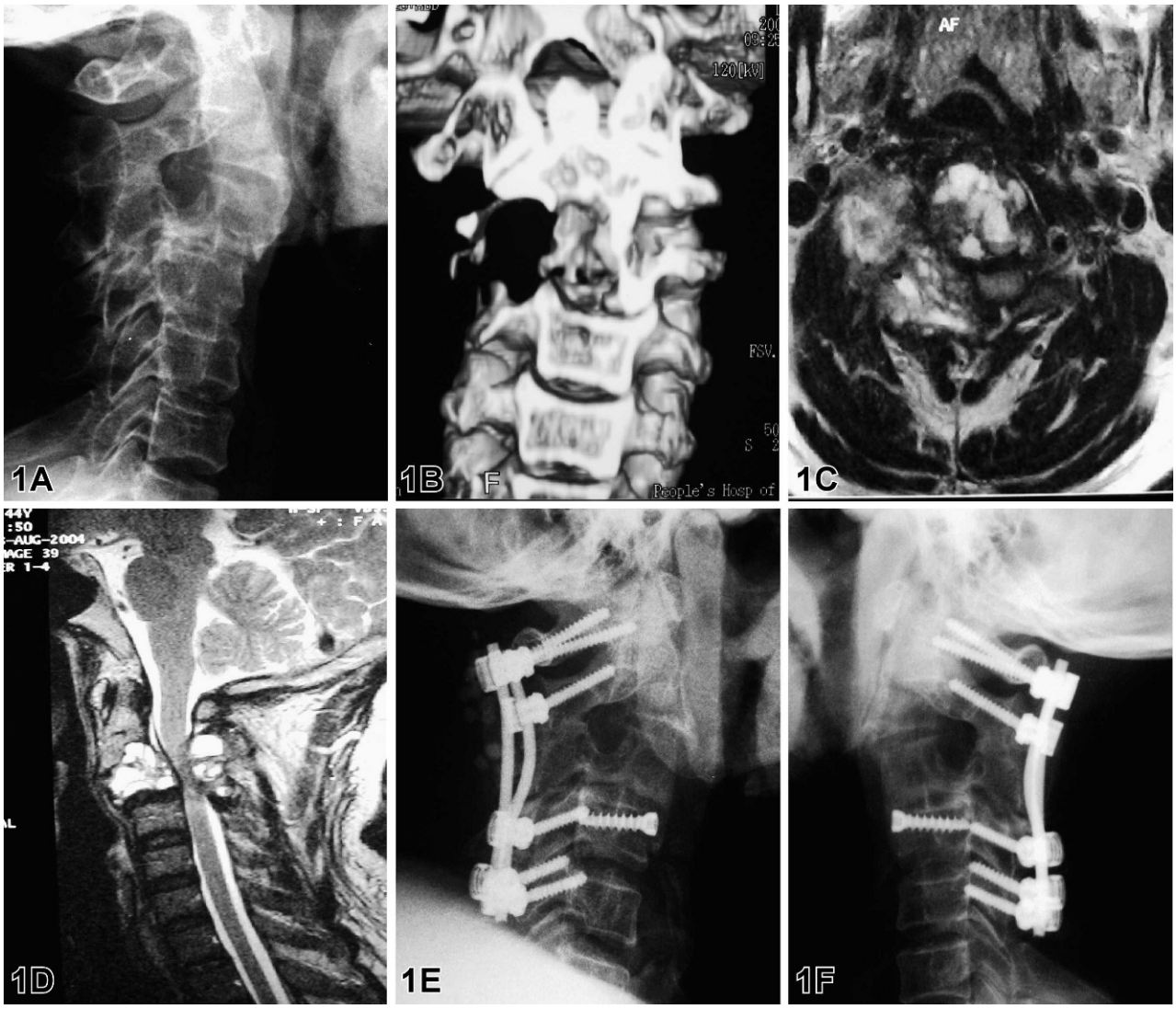

Fig. 1 Images of the first surgery of C2 to C3 intraosseous tumor in the cervical spine. An osteolytic lesion in the cervical spine is shown on lateral radiographs (A) and computed tomography coronary reformatted image (B). T2 weighted axial (C) and lateral (D) magnetic resonance images show inhomogeneously hyperintense mass. Postoperative lateral (E) radiograph shows the C3 anterior cervical corpectomy with strut iliac crest autograft supplemented with a screw fixation, and posterior autograft and calcium phosphonate fusion with a cervical pedicle/lateral mass screw and rod fixation from C1 to C5. Postoperative 6-month follow-up lateral (F) radiograph shows C3 anterior cervical corpectomy with strut autograft fusion and a satisfactory spinal fixation.

The right pedicle, laminar, and spinal process were destroyed and a soft tissue mass was extended from the C3 vertebral body to the right spinal canal and paravertebrae (Fig. 1B). T2 weighted images showed an inhomogeneously hyperintense mass involving in the C3 and partial C2 vertebral body, displacing the spinal cord, and extending the spinal cord posteriorly (Fig. 1C and 1D).

After combined pedicle and lateral mass fixation at C1 through C5 with the screw and rod system, the patient underwent removal of the posterior C2 to C3 tumor and an implantation of autograft and calcium phosphonate posteriorly. The anterior C3 tumor was resected by piecemeal method through an anterior cervical approach. Subsequently, a strut iliac crest autograft was tamped into the C2 through C4 vertebral body and the construct was supplemented with 1 screw (Fig. 1E). Six months postoperatively, it had bony fusion and maintained good fixation (Fig. 1F). Two years postoperatively, MRI showed that the tumor had relapsed and an inhomogeneous hyperintense signal mass in the C3 vertebral body

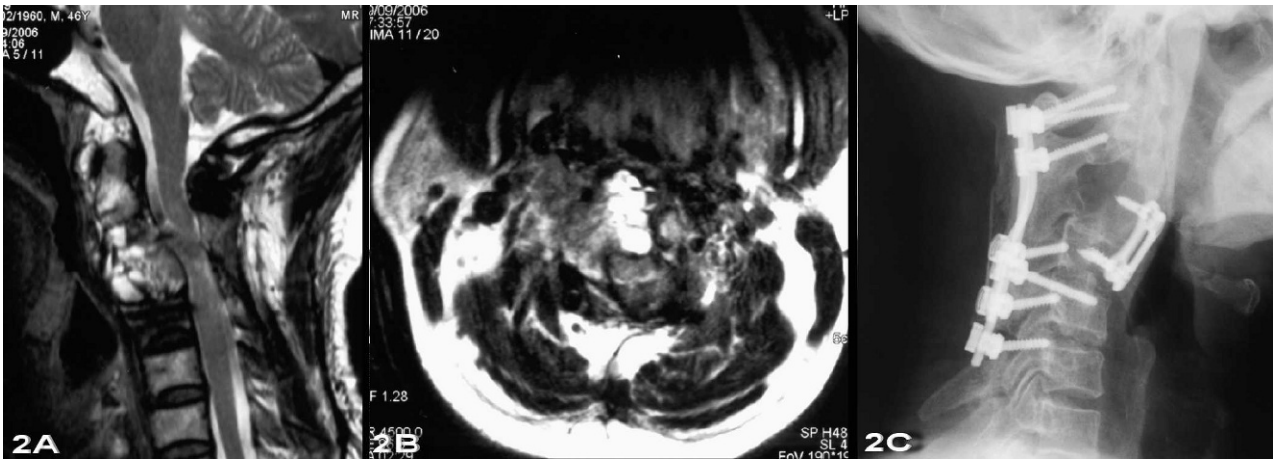

Fig. 2 Images of the second surgery for recurrent C2 to C3 intraosseous tumor in the cervical spine. An inhomogeneously hyperintense mass is shown on T2 weighted sagittal (A) and axial (B) magnetic resonance images at the C2 to C3 level 2 years after the first operation. After second resection, lateral (C) radiograph shows the C3 anterior cervical corpectomy with strut iliac crest autograft supplemented with a self-locking plate and screw system, and posterior cervical pedicle/lateral mass screw and rod fixation from C1 to C6.

expanded to the spinal canal and impinged the spinal cord (Fig. 2A and 2B). The surgical technique used was similar to the one described at the first operation. The construct was supplemented with 1 self-locking plate and screw system after a strut iliac crest autograft was tamped into the C2 to C3 vertebral body (Fig. 2C). Unfortunately, the tumor recurred in the C3 vertebral body 9 months after second surgical resection; MRIs revealed hyperintense signal (Fig. 3A and 3B). Due to rapid recurrence, the patient gave up surgical treatment and went to another institute for proton therapy. Ten months after receiving proton therapy, on MRI the tumor mass showed necrotic changes (Fig. 3C). The patient was asymptomatic at recent follow-up.

The patient had no stigmata of neurofibromatosis and reported no family history of the condition.

Histopathology and immunochemistry

Histopathology in the primary specimen from the preoperative biopsy and intraoperative resected tumor showed atypical features of benign schwannoma with high cellularity composed predominantly

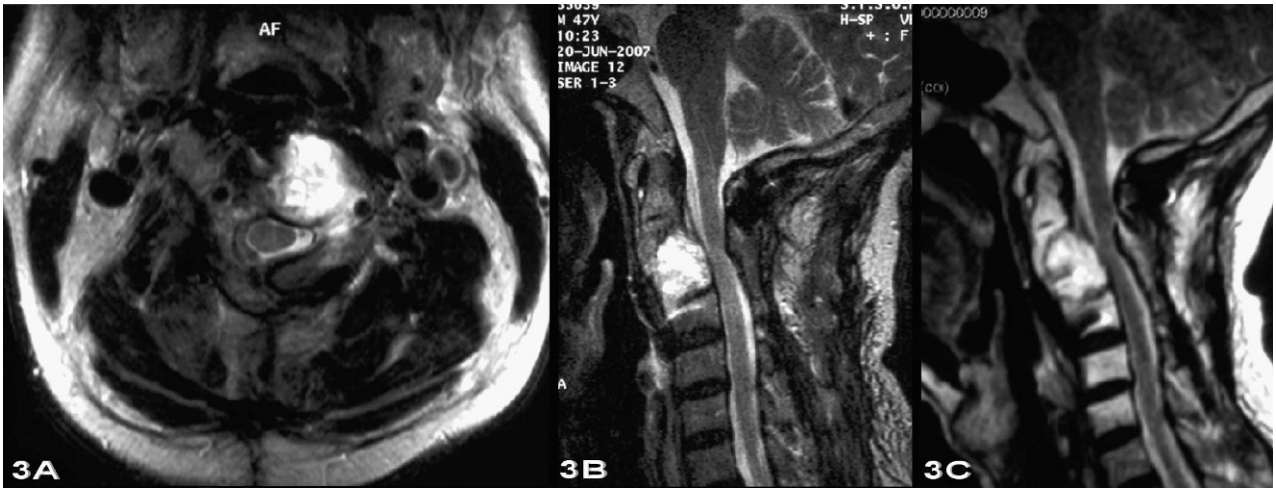

Fig. 3 Images of recurrent C2 to C3 tumor after the second resection and receiving proton therapy. An inhomogeneously hyperintense mass is shown on T2 weighted axial (A) and sagittal (B) magnetic resonance images in the C2 to C3 vertebral body 9 months after the second operation. The lesion had necrotic change on the T1 weighted sagittal section with gadolinium enhancement (C) after receiving proton therapy for 10 months.

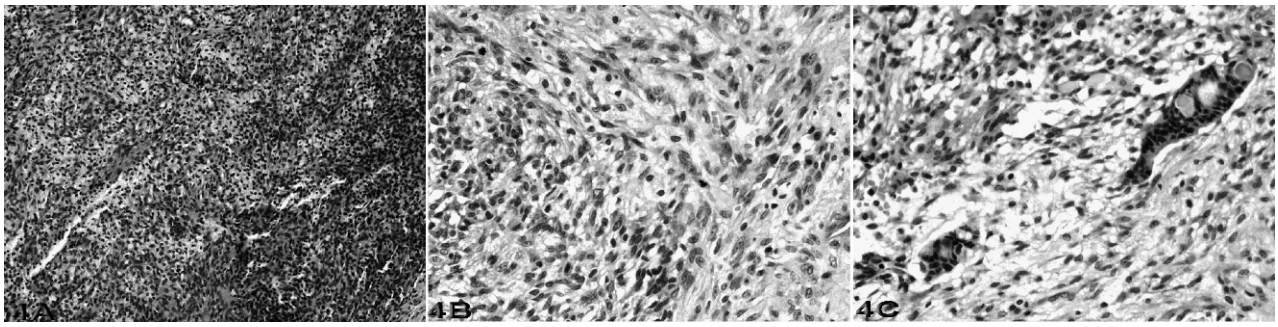

Fig. 4 Histopathologic examination. Histologic specimen of original intraosseous tumor showing atypical benign schwannoma with hypercellularity composed predominantly of Antoni A areas (A) (×200). Histologic specimen of recurrent intraosseous tumor showing scattered atypical spindle cells with pronounced pleomorphism and mitotic activity (B) (×400) and glandular formation, compatible with a malignant schwannoma (C) (×400).

of Antoni A areas that lack Verocay bodies (Fig. 4A). Malignant transformation was noted in the recurrent resected specimens, which showed atypical cellularity of spindle cells with pronounced nuclear pleomorphism, mitotic activity (Fig. 4B), and epithelization (Fig. 4C).

For immunohistochemical staining examination, confirmatory S-100 protein was strongly expressed by most cells in the primary tumor (Fig. 5A); however, a small number of positive staining cells were seen in the recurrent tumor (Fig. 5B). In the primary tumor, only 1% were positive Ki-67 staining cells (Fig. 5C), whereas positive p53 staining cells were less than 1% (Fig. 5D). Recurrent tumor had a high percentage of positive cells with Ki-67 staining in approximately 75% (Fig. 5E) and p53 staining in 80% (Fig. 5F).

Discussion

Schwannoma is a benign nerve sheath tumor, most commonly located in soft tissue. Spinal schwannomas

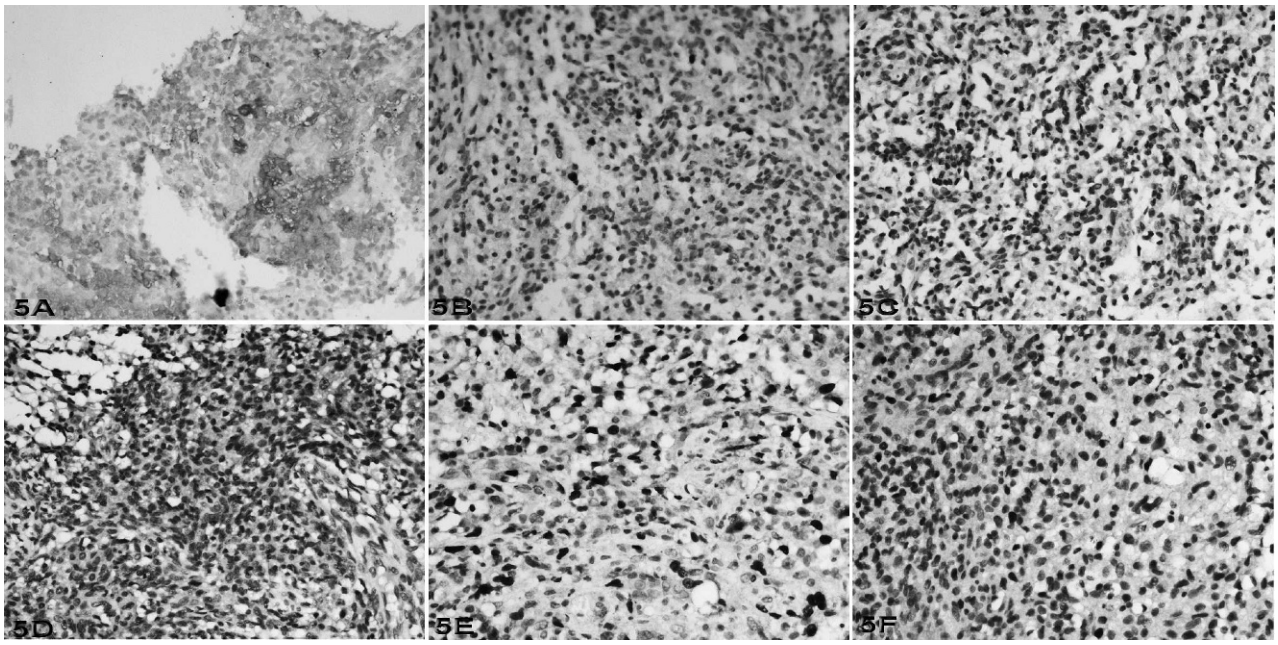

Fig. 5 Comparisons of immunohistochemical staining for S-100 protein, Ki-67, and p53 before and after malignant transformation. Before malignant transformation, immunohistochemical staining is shown with S-100 strongly positive (A), few Ki-67 positive cells (B) (×400), and p53 positive (C) (×400). After malignant transformation, it shows a small number of cells with S-100 positive (D), most cells with Ki-67 positive (E) (×400), and p53 positive (F) (×400).

compromise approximately 25% of all spinal tumors.[2,23] Occasionally, schwannomas involve osseous structures.[7,24] The patients with giant invasive spinal schwannomas had erosion of the cervical vertebral body, and it extended posteriorly and laterally into myofascial planes (giant invasive tumors, type V)[9] or (Toyama classification, type VI).[25] A significant degree of aggressive, expansile, osteolytic lesions in the cervical spine and its accessory structure did occur. The mechanisms of schwannoma involves the bone: (1) an extraosseous tumor causing secondary erosion, (2) tumor arising centrally within the bone (intraosseous schwannoma), and (3) tumor arising in the nutrient canal and growing in a dumbbell-shaped configuration.[26] Accordingly, a possible explanation for bone expansion in our patient is due to erosion of vertebrae by the tumor tissue with subsequent aggressive destruction within the vertebral body or due to the growth of the tumor along the spinal nerve branch.

The histopathologic features of malignant progression in our patient is an atypical cellularity, nuclear pleomorphism with high mitotic activity, and epithelioid differentiation in the recurrent tumor, which are consistent with reports primary spinal malignant schwannoma[14] and malignant transformation arising in benign schwannomas.[17] Epithelioid malignant change is characterized by scattered single large epithelioid cells in a benign schwannoma, the cells being morphologically similar to cells of epithelioid MPNST, which is not associated with neurofibromatosis type 1. Epithelioid malignant change is also recognized in which epithelioid MPNST arose in a schwannoma.[16] The tumor described in our patient is considered to be a rare example of benign invasive intraosseous schwannomas in the cervical spine with recurrent malignant transformation. Because histopathology in the primary specimen showed atypical features of benign schwannoma, it suggested that atypical features of benign invasive intraosseous schwannomas might have the possibility to transform malignantly.

Immunohistochemistry was useful for establishing the diagnosis in our patient. Usually benign schwannoma, as well as its cellular variant, is diffusely positive for S-100 protein, whereas less than 50% of MPNSTs present only focal staining in limited areas. There were many positive cells with S-100 protein in the primary tumor, but only a small number of positive staining cells were seen in the recurrent tumor. p53 protein expression and proliferation marker Ki-67 on atypical cells was supportive in the evidence for malignancy. Malignant transformation may be also detected in some cases by p53 and proliferation marker Ki-67 before overt histologic evidence of malignancy.[27] The percentage of patients with positive immunoreactions of p53 was high in those with malignant schwannoma (100%).[28] The local recurrence, nuclear pleomorphism, and especially the high percentage of positive cells with p53 (80%) and Ki-67 (30%) antibodies support the aggressive nature of the lesion.[29] Neurofibromas and schwannomas displayed similar courses, but the clinical features of typical and cellular tumors were not the same. The mean age of the patient (56 years) with a schwannoma with malignant transformation was 2 decades older than conventional MPNST.[17] Cellular tumors with high scores were more disposed to recur and to undergo malignant transformation. Recurrences in cases of late malignant transformation were more frequent than in those showing no transformation.[30] The high percentage of positive cells with p53 (80%) and Ki67 (75%) in recurrent sample of malignant transformation in our case also was found. These results suggest that malignant transformation of intraosseous schwannoma may be induced by a mutation of the p53 gene, as p53 protein has been immunohistochemically detected in MPNST cells but not in tumor cells of the neurofibromatosis.

Early diagnosis and total surgical extirpation represent the optimal management for achieving both local control and recurrence. The imaging findings did not help in distinguishing between benign tumors and malignant transformation. Confirmatory differential diagnosis should be followed by histopathologic and immunohistochemical examinations. Because of the locally invasive nature and extensions in all directions of giant invasive intraosseous schwannomas, careful preoperative planning of the surgical approach is very important. For the surgical resection in our patient, we chose a combined one-stage posterior and anterior approach for successful removal of the tumor where the giant intraosseous schwannoma in the cervical spine extended widely through the intervertebral foramen beyond the region of the vertebral artery. Because the patient was readmitted for local recurrence 2 years postoperatively, there was a need for repeat surgeries. From the developmental process, it suggested that a C3 vertebrectomy at the first procedure would have help to avoid the recurrent lesion. Total spondylectomy may be a proper choice for treatment of a giant invasive intraosseous schwannomas.

In summary, we have presented an example of recurrence and malignant transformation in benign

intraosseous schwannoma in the cervical spine. The local recurrence, nuclear pleomorphism, epithelioid differentiation, and especially the high percentage of positive cells with p53 (80%) and Ki-67 (75%) proteins support the aggressive nature of the lesion in malignant transformation of benign intraosseous schwannoma in the cervical spine. Therefore, it is vital to recognize the nuclear pleomorphism and use the panel of antibodies, anti-S-100 protein, p53, and Ki-67, to identify progression and malignant transformation of benign intraosseous schwannoma in the cervical spine. It is our practice to suggest that such cases have to be carefully resected and followed up.

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