Case Report

An urban legend: Malignant transformation caused by radiotherapy in patients with presacral ganglioneuroma. The necessity and first-time administration of radiotherapy. Case report and literature review

ABSTRACT

Ganglioneuromas (GNs) are well-differentiated, rare benign tumors of neural crest origin and are, for the most part, considered to be the benign equivalent of neuroblastomas. There are very few cases of GN reported to be at presacral location in the literature. The standard form of treatment is the total surgical excision. However, total resection of GN is not always possible depending on the neuron, from which it originates, and its localization. Moreover, adjuvant radiotherapy (RT) or chemotherapy is not recommended even though patients are still symptomatic after subtotal resection. This view is based on the urban legend that it undergoes a malignant transformation although it is a benign tumor. Moreover, there are no data indicating that the GN cases reported in the literature have undergone RT. Therefore, articles about the suspicion that GN may undergo spontaneous or malignant transformation after RT are absolutely controversial. Based on our case, we present here, we believe that we will explain the valid necessity of application of RT that we administered for the first time and that with the clarification of this controversial topic, a significant gap will be closed in the literature.

KEY WORDS: Ganglioneuroma, malign transformation, radiotherapy

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INTRODUCTION

Ganglioneuromas (GNs) rarely develop, especially in the presacral location and the number of cases reported in the literature, including our case, is only 25 [Table 1].[1-19] Historically, these tumors have been categorized into three basic morphologic categories according to the International Neuroblastoma Pathology Classification system: neuroblastoma, ganglioneuroblastoma (GNB), and GN.[20] GN includes mature sympathetic ganglion cells and Schwannian stroma without neuroblasts or intermediate cells, neuroblastoma includes immature elements (primitive neuroblasts), and GNB has an intermediate cell population with both mature and immature cells.[20,21] There is an urban legend in the literature that GN undergoes a malignant transformation. This view was first introduced by Cushing and Wolbach in 1927.[22] Since then, two more cases have been added in 1988 and 2015. Nevertheless, the malignant transformation could not be fully proven. Due to this false belief, there have been hesitations to administer other treatment options such as chemotherapy and radiotherapy (RT) in these tumors. In these patients with prolonged survival, in cases where a complete surgical resection is not possible, undesirable deficits may happen and disrupt the quality of life of patients if resection limits are pushed. RT can be an alternative or well-planned combined treatment option that can prevent functional losses in these patients.

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Table 1: Clinical, surgical, and radiotherapy data in our patient and 24 previously reported cases

Case number	Author, year	Age	Size (cm)	Symptoms	Resection	RT	Follow-up
1	MacCarty *et al*., 1965[1]	37/male	6	Pain	C	No	Asymptomatic after 9 years
2	Andersen *et al*., 1986[2]	14/male	No data	Pain, acute appendicitis	ST	No	Asymptomatic after 2 years
3	Richardson *et al*., 1986[3]	71/male	No data	Neurogenic bladder, constipation	ST, second surgery	No	Postoperatively, improved urination afterward
4	Leeson and Hite 1989[4]	21/male	No data	Dysuria, left leg numbness	ST, second surgery	No	Asymptomatic after 3 years
5	Stener 1989[5]	20/female	No data	Pain	C	No	Asymptomatic after 20 years
6	Spirnak and Wood 1993[6]	8/male	13×8×5	Progressive constipation	C	No	Asymptomatic
7	Okai *et al*., 2001[7]	70/male	9×5×4	Flank pain, constipation, weight loss	C	No	Mild constipation persisted
8	Lam and Nagib 2002[8]	11/male	No data	Back pain, constipation	C	No	Asymptomatic after 4 years
9	Marmor *et al*., 2002[9]	70/female	6×5.5×6	None	C	No	No data
10	Modha *et al*., 2005[10]	65/female	9×3	Bilateral hip pain	ST	No	Asymptomatic after 2 years
11	Modha *et al*., 2005[10]	21/female	12×7	Severe flank pain	ST	No	2 years no recurrence, chronic foot pain
12	Modha *et al*., 2005[10]	21/male	5	Asymptomatic	ST	No	3 years no recurrence, chronic foot pain
13	Modha *et al*., 2005[10]	19/female	8	Low back pain, constipation	C	No	18 months asymptomatic
14	Modha *et al*., 2005[10]	28/female	No data	Low back pain	ST	No	Asymptomatic after 6 years
15	Przkora *et al*., 2006[11]	17/female	No data	Amenorrhea, weight loss	C	No	Asymptomatic after 2 years
16	Cerullo *et al*., 2007[12]	64/male	12×9×8	Asymptomatic	C	No	Asymptomatic after 8 months
17	Mounasamy *et al*., 2006[13]	64/male	13.5×8.2×5.6	Low back pain, thigh pain	C	No	Asymptomatic after 12 months
18	Mounasamy *et al*., 2006[13]	21/female	10×8×7	Asymptomatic	ST	No	Asymptomatic after 4 years
19	Roganović 2010[14]	12/female	9×8×7	Lower abdominal pain	C	No	Asymptomatic after 3 years
20	Vardas *et al*., 2013[15]	35/male	10.5×8×4	Abdominal pain	C	No	Asymptomatic after 2 years
22	Lynch *et al*., 2013[16]	42/female	12×6×8	Lower back pain	C	No	Asymptomatic after 2 months
23	Variya *et al*., 2015[17]	2/male	6.3×6.2×7.0	Lower abdominal pain, pelvic mass	No data	No	No data
24	Holz *et al*., 2013[18]	31/female	5.3×3.7×4	Asymptomatic	C	No	Asymptomatic after 1 year
21	Lee *et al*., 2017[19]	47/female	3.4×2.4×4.5	Pain, tingling sensation on thigh	C	No	No data
25	Present case	56/female	2.34 cm^3	Pelvic pain, inability to walk, constipation	ST	Yes	Postoperatively neurological deficit improved, costipation, persistent urinary incontinence symptomatic during 3 years

C=Complete resection, ST=Subtotal resection, RT=Radiotherapy

CASE REPORT

A 55-year-old female patient had back pain, pain in both hips, and an ever-increasing constipation complaints for 2 years. For all procedures involved in the diagnosis and treatment of the patient obtaining consent beforehand is compulsory in our establishment. She presented to a medical institution with also the complaint of inability to walk that emerged in the last 1 year. In the pelvic magnetic resonance (MR) and computed tomography (CT), a mass was discovered at the S1–S2 level extending to the presacral area [Figure 1a, d, and g]. A decision was made to conduct a biopsy as the appearance was initially thought to be a malignant tumor originating from the entire anterior sacrum, with sporadic invasions on the sacrum bone. The result of the incisional biopsy was reported to be GN. Pathologically, the tumor showed diffuse S100 positivity, synaptophysin was positive in ganglion cells, and Ki-67 proliferation index was low (1%). The second operation was planned after the patient's hip pain became intolerable and after learning that the pathology of the lesion was benign. The pain was thought to be due to the crushing of the S1 nerve root. A total laminectomy was performed on the posterior wall of the sacrum of our patient under spinal anesthesia. During the operation, it was seen that S1, S2, and S3 nerve roots were extremely hypertrophic [Figure 1f], and because of this growth, the nerve roots were crushed in the spinal canal. The deformed section of the left S2 root that extended into the anterior section of sacrum was excised. All the pain of the patient was gone immediately after the surgery. No motor deficit was observed. However, on the 2nd postoperative day, it was understood that our patient was unable to urinate. A catheter had to be inserted. Bladder exercises were done, and medicines to help different sphincter controls were used for a long time. Preoperative, postoperative, and intraoperative images of our patient are seen in Figure 1.

Microscopic examination of the main extracted specimen

The mass was encapsulated and measured to be 1.5 cm × 1 cm

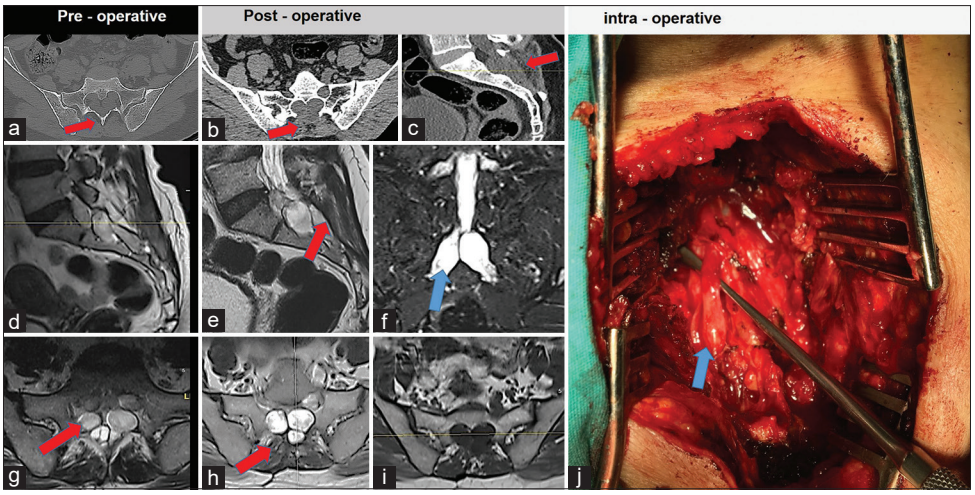

Figure 1: Preoperative, postoperative, and intraoperative images of the case. (a) The lamina that covered the posterior sacrum appeared to have been thinned in the preoperative axial computed tomography image. Foramina in the sacrum appeared to be regularly wider and greater than the normal, based on the diffuse growth of the nerve roots. (b and c) A mass was visible in the computed tomography image, extending from the neural foramina of the sacral spinal area into the presacral area. The pelvic computed tomography showed an occlusion defect toward posterior at the sacral level and large-scale expanded nodular mass lesions in the neural foramina. After the surgical decompression, the sacrum lamina was not observed in the area marked with red arrows. (e-j) in the postoperative magnetic resonance, a mass lesion was visible, extending from the neural foramina of the sacral spinal area into the presacral area. (d) A mass lesion was visible on the sagittal T2-magnetic resonance image. (e) On the sagittal T2-magnetic resonance image, a mass extending from the neural foramina of the sacral spinal area to the presacral area was visible, which was expanding toward the posterior and upwardly following the surgery. (f) In the turbo-spin-echo sequence, the lumbar spinal S1 root appeared to be quite large. (g) The right S2 sacral spinal nerve root was visible on the axial T2-magnetic resonance image section. (h) After the removal of sacrum lamina, the sacral nerve roots appeared to have shifted posteriorly. Because a piece of the S2 nerve root was extracted to get the true diagnosis, the right S2 nerve root was not visible. (i) The lesion appeared to have no contrast on the contrast-enhanced T1-magnetic resonance image section. (j) In surgical view, the right S2 nerve root appeared to have diffusely grown in every direction

in size. The cut surface was homogeneous and soft to firm in consistency with no hemorrhage or necrosis.

Microscopic examination

The histopathology revealed a biphasic tumor with ganglion cells and Schwannian stroma. The ganglion cells were mature with eccentric nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The immunohistochemical evaluation revealed diffuse S100 protein positivity, and the mature ganglion cells were synaptophysin positive. The tumor showed a low Ki67 proliferation index. No undifferentiated component was seen in the tumor. The final diagnosis reported GN [Figure 2].

Considering the possibility of malignancy, a positron emission tomography-CT (PET-CT) examination was planned, as the MR and CT examinations of the patient revealed a progressive lesion and significantly increased symptoms. The FDG uptake was within normal range in the lesion area at the sacral foramina level in the PET-CT. The fluorodeoxyglucose (FDG) uptake pattern compared to the medulla spinalis was heterogeneous and minimally increased in the lesion area [Figure 3]. Maximum standardized uptake values (SUVmax) for medulla spinalis and the tumor were measured to be 1.2 and 1.6, respectively. The metabolic volume of the tumor with an SUVmax value >1.2 was calculated to be 2.34 cm^3. We think that especially this piece of data

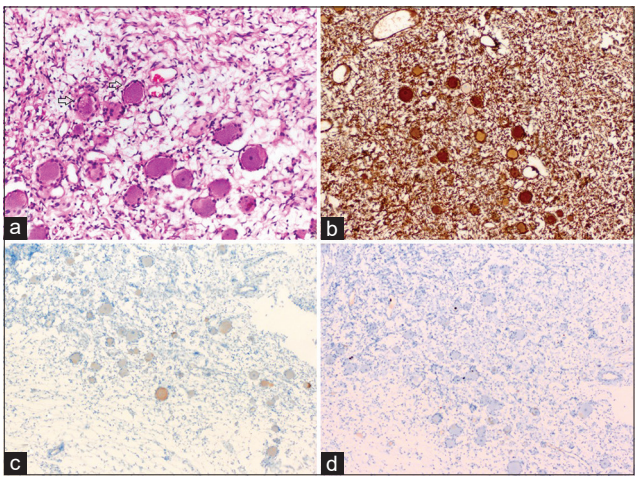

Figure 2: Pathological view. (a) Tumor composed of mature ganglion cells (black arrow) within Schwannian stroma (H and E, ×200). (b) Tumor showing diffuse S100 protein positivity (×200). (c) Mature ganglion cells with synaptophysin (×200). (d) Tumor showing low proliferation index (Ki-67 <1%)

can be used to facilitate defining a location for biopsy and planning RT. In GN cases, if there is an area in the lesion with an increased level of FDG uptake, this is considered to be risky for malignancy[23] and it is recommended that a new biopsy should be conducted on such an area. In our case, the uptake pattern in the PET-CT did not suggest malignancy; therefore, a new biopsy was not considered.

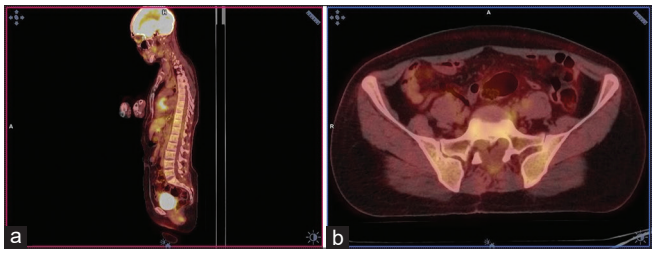

Figure 3: Positron emission tomography-computed tomography images of our patient. (a) Axial fused positron emission tomography-computed tomography of the pelvis (ganglioneuromas at the level of sacral neural foramen). (b) Sagittal-fused positron emission tomography-computed tomography image

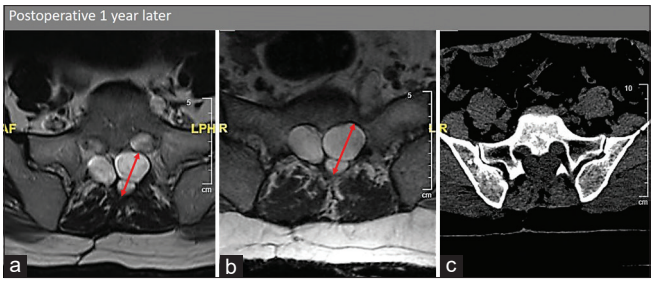

Figure 4: The images where the progression was detected. (a) The diameter of the widest section of the tumor was 21 mm on the magnetic resonance images that were obtained approximately 1 year ago. (b) The widest diameter of the mass was measured to be 24 mm on the magnetic resonance image that was obtained at the time of the study. (c) The destruction that the tumor created in the sacrum was visible in the new computed tomography image

The radiological follow-up of the patient was with MR for 1 year after the surgery. At the end of this period, it was observed that the tumor grew radiologically even though it was a benign tumor [Figure 4]. Moreover, with the onset of pain related to the S1 root clinically, the patient was decided to be evaluated for RT as a result of the search for treatments that could stop tumor growth.

A third resection was not planned as the patient was still having problems with controlling urination and as a new surgery might disrupt the neurogenic bladder and stool control. Since the lesion was progressive and the patient complained of pain and urinary incontinence, RT was offered as a treatment option by also considering the fact that a new surgery was not performed. Based on the RT guides for nonmalignant diseases,[24,25] it was considered that sufficient and valid grounds were present for this patient. The patient was informed verbally and in writing, and RT was suggested after her permission was received.

Table 2: Principles of application of radiotherapy for nonmalignant diseases

1. Estimate the natural course of disease without therapy
2. Consider potential consequences of nontreatment of the patient
3. Review data about alternative therapies and their therapeutic results
4. Conduct a risk-benefit analysis compared with other possible measures
5. Proof that the indication is justified: if conventional therapies have failed, if risks and consequences of other therapies are greater, and if nontreatment has more dramatic consequences than irradiation
6. Consider the individual potential long-term radiogenic risks
7. Inform patient about all details of RT: target volume, single/total dose, duration of session and series, relevant radiogenic risks, and side effects
8. Written consent of the patient following thorough patient education
9. Assurance of long-term aftercare to document result
10. Request a competent second opinion in case of doubts and if the provided patient data or treatment decision are uncertain

RT=Radiotherapy

The valid ground for radiotherapy

RT is known to be used successfully also in nonmalignant diseases. In benign diseases, RT generally works through a complex interaction of different effects on many cell types not through a single or certain mechanism. In nonmalignant disorders, RT is considered in three groups: painful degenerative skeletal disorders, hyperproliferative disorders, and symptomatic functional disorders.[25] Our case can be counted in the second one of these listed groups. Because nonmalignant diseases may cause pain or other serious symptoms and thus have a permanent effect on the quality of life, RT can be administered if there are no other treatment methods or if a treatment method has been unsuccessful or may cause more side effects. The principles of RT of nonmalignant diseases have sufficiently been defined in the international literature, and they can be summarized in ten items [Table 2].[24]

When our patient was evaluated in terms of these principles, the disease was progressive in its natural course. If the disease was not treated, it was thought that there was a high possibility of development of a neurological deficit (the patient was unable to walk after the first surgery). There were no alternative treatments for the disease other than surgery, and because of the prevalence of the lesion, surgery was not viable. Performing a radical surgery could possibly cause more functional loss than RT toxicity could cause. Under these conditions, there was no treatment option, other than RT, to be administered and to provide dramatic benefits. Considering the patient's RT toxicity, we had the capabilities to minimize the dosage in risky organs with the help of highly technological treatment techniques such as intensity-modulated radiation therapy and volumetric-modulated arc therapy (VMAT). Our 57-year-old patient did not have a concern for fertility, either. Based on all this information, it was concluded that RT could be offered as a treatment option in the case of this patient.

A decision was made to administer RT after the patient was informed and her written approval was received. However, there was no such case receiving RT in the literature, so a dose of 43 Gy, which was administered by Okudera *et al*.[26] in GNB as the RT dose, was taken as a reference. This dose was administered for a postoperative microscopic disease. For this reason, it was necessary to administer a dose that was greater

than that. Moreover, RT doses that have been administered in benign and slowly progressive tumors such as desmoid tumors were also examined. A dose of 50 Gy is recommended in completely resected desmoid tumors. A dose of 56–58 Gy is recommended if only RT is administered.[27] Thus, it was decided to administer a dose of 56 Gy in our patient. The gross tumor volume (GTV) of the contoured tumor region located at the S1, S2, and S3 nerve roots was formed by fusing together the PET-CT, MR, and CT images. The clinical tumor volume (CTV) was formed by setting a 1-cm margin from the top and bottom of the other part of the nerves remaining in the sacrum [Figure 5]. GTV and CTV were ensured to be 56 Gy and 50.4 Gy, respectively, with a daily dose of 200cGy in 28 fractions and 5 days/week using the VMAT Simultaneous Integrated Boost technique in the Eclipse Treatment Planning System of the Varian Trilogy Device. The doses of the risky organs such as the bladder, rectum, and intestines were ensured to be low. Figure 5 shows the three-dimensional isodose and dose-volume histograms of our patient.

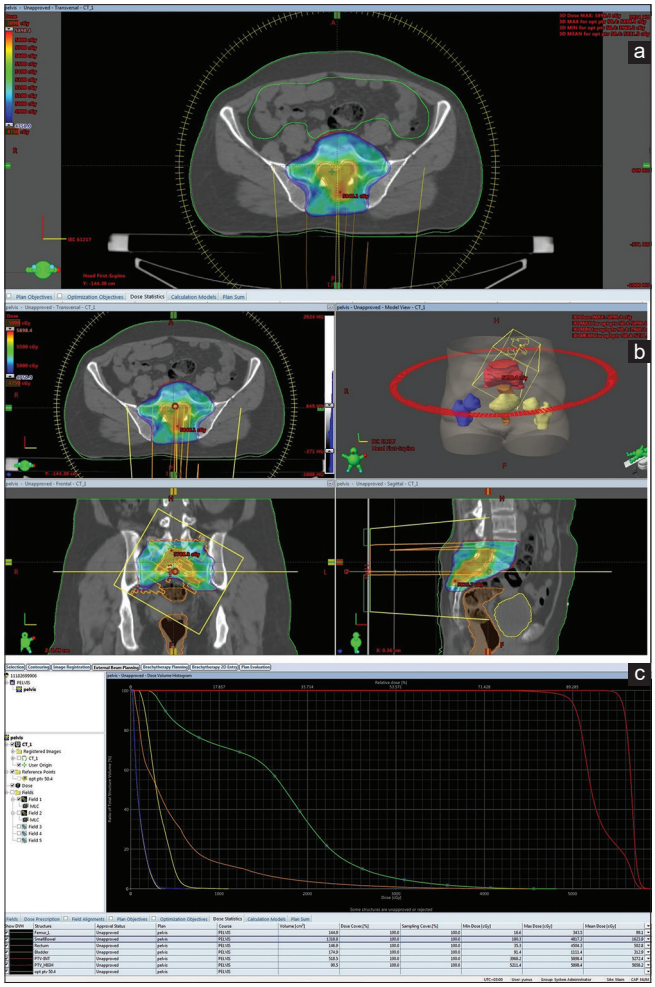

Figure 5: Dose and area images of the radiotherapy. (a and b) Dose distributions at the axial, coronal, and sagittal planes and three-dimensional reconstruction of the radiotherapy plan. (c) The dose-volume histogram showing the doses received by the targeted and risky organs

DISCUSSION

In adults, presacral and sacral tumors are uncommon lesions with an incidence rate of approximately 1/40,000 admissions.[28] GN of the peripheral nervous system was first described in 1870.[4] The tumors usually show a slow-growing pattern with a predominance in women.[29] Most tumors are diagnosed at their progressed state in patients between 10 and 30 years of age because symptoms only appear when the mass becomes large enough to exert a mass effect.[30,31] It has been stated that the median age at the diagnosis is 35.5 years for the presacral location.[32,33] The only known treatment modality is surgery. A subtotal surgery was performed on ten of the cases reported in the literature, and two of these patients needed a second surgery [Table 1]. The most common symptoms patients have are pain and constipation, while the other symptoms include neurogenic bladder, dysuria, weight loss, amenorrhea, and a tingling sensation. Our patient complained of inability to walk, constipation, and pain.

As indicated in Table 1, none of the cases reported in the literature have taken RT. Subtotal excision has been administered as the treatment. Adjuvant treatment has not been planned despite persistent symptoms after surgery. Because the disease is very slowly progressive, patients live for many years. The fact that they live in a symptomatic way seriously disturbs the quality of their lives. Regarding the role of RT in GN and GNB, Benderli Cihan *et al*.[33] indicate that "surgical excision is the primary treatment but in inoperable, unresectable, and metastatic cases, RT should be considered for symptom palliation associated with metastatic masses." In GNB located in filum terminale, because of residue after resection, RT was administered with a dose of 43 Gy over 4 weeks. No residue was found in the MR and CT scans of this patient after RT. Moreover, neurological symptoms gradually improved and at the end of the radiation therapy, the patient was able to urinate without a catheter and walk with a crutch. Among the series of six diseases in this article, this patient was the only patient to receive RT and had the longest lifespan, which was 19 years.[26]

Cerullo *et al*.[12] have reported that "some authors reported malignant transformation, spontaneously or after RT." However, there were only two articles that were referred to in this respect.[20,22] When these were examined, it was found that almost all of the publications, including a study of Shimada *et al*.[20] referred to the article written by Cushing and Wolbach[22] In that study, the story of a 2-year-old child who referred to a health-care institution for lumbar swelling after trauma and who was initially diagnosed with a sarcoma (malignant tumor, "a spindle celled sarcoma") is the case. After surgery, this child was treated with adjuvant Coley's toxin. With this treatment, the growth of the tumor stopped, but paraplegia became permanent. After a 10-year latent phase, when the child was reoperated for paraplegia, the child was diagnosed with cellular sympathicoblastoma (sympathetic

neuroblastoma). Although this tumor was claimed to have transformed from GN after the first operation, the claims are very weak and doubtful. The case is quite controversial. The initial pathological diagnosis was a malignant tumor, "a spindle celled sarcoma." There are not sufficient data about the location and the surgery of the tumor. The patient was treated with Coley's toxin, which was used in the 1980s and can be considered a treatment similar to the present time immunotherapy, not RT.

Another study claiming the malignant transformation of GN is the study of Kulkarni *et al*.[34] published in 1982. This case was a 21-year-old patient operated for a retroperitoneal mass and had a pathology reported to be GN. The clinical and surgical details about the first operation of the patient were not specified. The patient was reexamined 11 years later at the age of 32 because of the development of neurological symptoms. A computerized tomography myelogram revealed a complete block at L-1 caused by an extradural mass that had a significant bilateral paravertebral extension and affected the L-1 vertebral body. An emergency laminectomy was performed, and after the second operation, the specimen was pathologically examined and reported to be neuroblastoma.[34] The pathology blocks from the first surgery of the patient were restudied, and the first pathology was confirmed to be GN. Although the author claimed that his study was the first report of the malignant transformation of GN into neuroblastoma, there is no information about the data of the first operation and the location of the lesion. It is doubtful that a case with neuroblastoma located at L-1 proves to be the malignant transformation of GN originating from an 11 years earlier retroperitoneal mass.

In a recent study claimed to prove the malignant transformation of GN,[35] a 22-year-old patient underwent an excision of a retroperitoneal mass located at T12–L3. The patient was reoperated 4 years after this operation because of relapse at the same location. While the pathology of the first operation was GN, the pathology of the second operation turned out to be GNB. When the first pathology specimen of this patient was reexamined, an undiagnosed cellular area with characteristics of GNB was found in a small area, and its pathology was considered to be GNB. This patient was reoperated after 9 years for an extradural mass located at T10. The pathology of this last specimen was reported to be neuroblastoma. While the GNB pathology of the first operation was located at T12–L3, the location that was reported to be NB 13 years later was T10. The location of these two tumors was not the same. What is more, the pathology of the first tumor was also GNB. Therefore, the claim that GN has undergone a malignant transformation is invalid in this case, too.[35]

CONCLUSION

These neurological tumors are known to exhibit various behaviors such as involution, spontaneous regression, maturation, and aggressive proliferation.[20] The mechanisms of these biological phenomena have not yet been fully understood. Due to predisposed genetic characteristics that are present, different neurological tumors independent of each other may also develop in patients over time. In conclusion, it could not yet be proven that GN, a benign tumor, has a potential to turn into neuroblastoma spontaneously or caused by RT after a latent phase of 10, 11, or 13 years. At present, surgery is the only treatment modality for this disease. Treatment modalities that are alternative or can be combined are needed because of the conditions where the treatment is insufficient. We think that guides for RT for nonmalignant disorders can be used as base, and thus, RT can become a viable treatment option in these patients. At the end of RT, the patient's complaints have been alleviated in the pain; furthermore, we think that it will be more impressive to overcome the patient's late results. This study is the first publication to refute the urban legend that GN undergoes a malignant transformation as well as being the first case involving RT in the literature.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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