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Ganglioneuroma Diagnosis 25 Years After Recurrent Neuroblastoma Treatment: A Case Report

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Introduction: Ganglioneuroma is a rare, well-differentiated benign tumor that originates from neural crest cells. It is asymptomatic and is diagnosed based on its compressive effects in the area of expansion. There is a possibility that ganglioneuroma originates from neuroblastoma.

Case Presentation: In this case report, we present a 28-year-old man with a history of neuroblastoma diagnosed at 45 days of age. Pathological results confirmed the diagnosis of neuroblastoma, the most frequent extracranial solid tumor in neonates and children; treatment included chemotherapy, radiotherapy, and mass resection surgery. At three years of age, he was diagnosed with the same tumor recurrence following urinary incontinence and poor defecation control. No further oncologic follow-up imaging was documented between ages 3 and 28. A soft tissue mass was discovered incidentally on preoperative imaging 25 years after treatment of the neuroblastoma recurrence, which showed a noticeable soft tissue mass in the spinal canal with extension to the anterior side of the sacrum and pelvis, and compression of the adjacent anatomy; biopsy of this lesion confirmed ganglioneuroma. Considering the absence of symptoms, the lesion was managed conservatively with clinical follow-up.

Conclusions: It could be suggested that ganglioneuroma in this patient may represent late maturation of the previous neuroblastoma, as noted in previous studies. However, a direct relationship between the two lesions cannot be established. Since the timing of any such maturation cannot be determined without continuous imaging surveillance, serial follow-ups may be needed after neuroblastoma diagnosis to detect any changes in the tumor.

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INTRODUCTION

Neuroblastoma (NBL) is an embryonal autonomic system tumor of neural crest origin [1]. The median age at NBL diagnosis is 17 months [2]. NBL is the most common extracranial solid malignant tumor during infancy, with an incidence rate of approximately 10.2 per million [3]. The tumors typically arise from the adrenal medulla or paraspinal ganglia of the abdomen, but they can also be seen in other areas of the autonomic nervous system, and their symptoms can range from asymptomatic to critical symptoms [2, 4].

NBL may cause huge morbidity and mortality in childhood cancers, even though the course of the disease may be self-limited with complete regression [5, 6]. According to the statistical database, while survival rates for localized tumors (stages 1–3) reached 91% by 2015, high-risk/metastatic cases (stage 4, >18 months) remained at 38% [7].

As was reported in some cases, malignant NBL maturation to benign ganglioneuroma (GN) has been suggested [8-10]. There have been several case reports in which transformation between NBL and GN happened; for example, there was a 28-year-old female case in which NBL was resected from the adrenal gland in childhood, and now the GN has been discovered in her pancreas gland [8]. Another case was reported with positive vanillylmandelic acid (VMA) and homovanillic acid, and a probability of NBL diagnosis that was not proved by imaging, etc., but 11 years later, a large presacral mass was discovered, which caused amenorrhea and weight loss and appeared to be GN [9].

Case Presentation

We present the case of a 28-year-old male who was found to have a pelvic mass incidentally, without any associated signs or symptoms. On the first visit, the patient had no abnormalities on examination except for an increased deep tendon reflex. All laboratory tests, including complete blood count, liver function tests, endocrine evaluation, VMA, and nephrology tests, were normal. There was also no positive family history of NBL.

The patient had a history of anuria on the 3rd day of his life during the neonatal period. At 45 days of age, following magnetic resonance imaging (MRI), solid tissue on the left side of the rectum, the posterior side of the bladder, and the medial side of the iliac crest, as a cemented area, was discovered that needed a biopsy for a definite diagnosis (Figure 1). The pelvic mass was fully resected, and the pathology result confirmed a diagnosis of neuroblastoma. Histopathological examination revealed small, round blue cells with scant cytoplasm and hyperchromatic nuclei, consistent with neuroblastoma. The tumor was staged as International Neuroblastoma Staging System (INSS) Stage 3. The tumor was histologically poorly differentiated with unfavorable histology, and pathology revealed small, round, blue tumor cells with a high mitosis-karyorrhexis index (MKI).



Figure 1. In Panels (A) (axial, T1-weighted images (WI)), (B) (coronal, T1WI), and (C) (Sagittal, T1WI), the markings show the pathology

At the age of three, following urinary incontinence and poor defecation control, paraclinical investigations were performed, and MRI reported a tumor recurrence and its erosion into the sacrum (**Figure 2**). Bone marrow biopsy was normal, and urine VMA levels were within the normal range. Following the recurrence, the patient underwent four cycles of chemotherapy consisting of Cisplatin (dosage: 80 mg/m² on day 1), Etoposide (100–150 mg/m² on days 1–3), and Vincristine (1.5 mg/m² on day 1). The patient also received fractionated

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radiotherapy (~2 Gy per session) to the sacral region, consisting of 20 sessions. These interventions resulted in tumor regression; however, complications such as testicular atrophy developed, and urinary incontinence

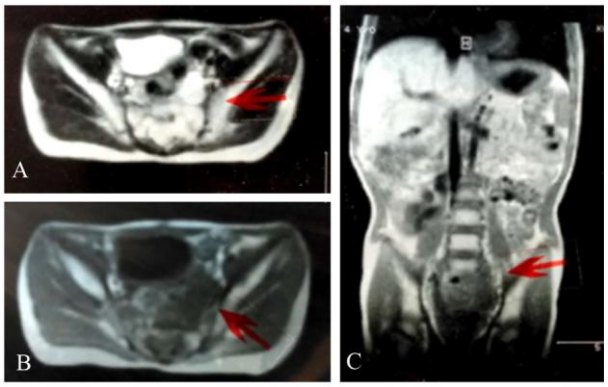


Figure 2. In Panels (A) (axial, postgadolinium T1WI), (B) (axial, T1WI), and (C) (coronal, T1WI), the arrows show the pathology.

persisted.

After the treatment of the recurrence at 3 years of age, the available clinical history indicates a prolonged period without documented symptomatic tumor progression. No intermediate assessment documenting the tumor status during this period was available. At 28 years of age, approximately 25 years after the treatment of the recurrent tumor, following a checkup after his herniorrhaphy surgery, the patient underwent a computed tomography (CT) scan, which reported destruction of the sacrum and widening of the spinal canal, and a noticeable soft tissue mass image in the spinal canal with extension to the anterior side of the sacrum and extension into the pelvis and an effect of compression on adjacent anatomy. Following these findings, lumbar and coccygeal MRI and lower-limb electromyography and Nerve Conduction Velocity (EMG-NCV) were performed. MRI demonstrated an extensive NBL V/S neurofibroma involving the lower part of L4 down to the distal sacrum, measuring 10.5 x 5 cm (Figure 3), and the main EMG-NCV finding was a chronic bilateral S1 to S4 root lesion with poor evidence of regeneration and no evidence of active denervation.

Following a consultation with a neurosurgeon, a CT-guided biopsy of the pelvic mass was performed. Pathological examination revealed mature ganglion cells and abundant Schwannian stroma, with no evidence of neuroblastic elements or mitotic activity, confirming the diagnosis of ganglioneuroma. The current lesion was located in the same region as the patient's original neuroblastoma and its documented recurrence. However, because there was no causal interference with the patient's everyday activities and lifestyle, and given the asymptomatic, benign nature of the mass, surgical treatment was not recommended, and conservative management with regular clinical follow-up was decided. The patient was followed for 12 months after diagnosis of ganglioneuroma, with no



Figure 3. Panels (A and B) (Sagittal, T1WI) show the latest MRI.

new symptoms or change in the mass reported.

DISCUSSION

NBL is the most frequent extracranial solid tumor in neonates and children and has also been presented in combination with Hirschsprung's disease, congenital hypoventilation disorder, and neurofibromatosis type 1 [11]. It is responsible for almost 8% of all reported malignancies in patients younger than 15 years old [12] and 15 percent of the mortalities in the pediatric population caused by cancers are accounted for. NBL may spontaneously relapse or progress, with or without therapies, or have a very aggressive, malignant phenotype that is poorly resistant to intense, multimodal therapy [12]. As we mentioned, NBL in our patient regressed after treatment of the recurrence, 25 years before the diagnosis of GN.

GN, on the other hand, is a well-differentiated, rare neural crest benign tumor, usually found in the posterior mediastinum, retroperitoneum, and adrenal gland. Presacral GNs are exceedingly rare and are believed to occur exclusively in females [13]. Patients are usually asymptomatic, and most tumors in patients between 10 and 30 years of age present with progressive tumors when symptoms appear only after the mass grows large enough to create a mass effect

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[14].

GNs develop from the embryonic neural crest originating from sympathoblasts. Histologically, it includes Schwann cells with a mature ganglion and is classified like NBLs and GN in the NBL group [13]. However, it is too rare for NBL to transform into GN, so a case study in 2016 described two infants with GN that developed from incompletely resected NBL [10].

In the early stage of our patient's presentation, in his infancy, signs, symptoms, and findings on MRI and biopsy led physicians to diagnose NBL, which was treated using several therapeutic procedures, including surgery, chemotherapy, and radiotherapy. Following treatment, there was no interruption to our patient's daily activities and occupation, and he lived for years without any symptoms.

Accidentally finding GN on a CT scan 25 years after the patient's last documented treatment for the recurrent NBL (at 3 years of age) raises two possible explanations: delayed maturation of the previous NBL or development of a primary GN, both of which are mentioned in papers [8, 10]. In the present case, several findings support a possible relationship between the two lesions. The original NBL arose in the pelvic region, subsequently recurred with sacral involvement at 3 years of age, and the current GN was identified in the same region. In addition, the initial lesion was definitively diagnosed histologically as poorly differentiated NBL, whereas the current lesion was definitively diagnosed histologically as mature GN. These findings are compatible with maturation of the original tumor; however, they do not establish clonality or prove that the current GN directly represents transformation of the original NBL. Therefore, the 25-year interval should be interpreted as the interval between the documented diagnoses/treatment of the recurrent NBL at 3 years of age and the subsequent diagnosis of GN at 28 years of age, rather than as the interval from the initial NBL diagnosis at 45 days of age or the documented duration of the maturation process. Long-term follow-up of patients with a history of neuroblastoma may be clinically relevant [9].

The transformation of NBL to GN is rare, and potential risk factors remain poorly understood. Some hypotheses include potential genetic, treatment-related, or immunological factors [15]. Further research is needed to identify specific biomarkers that can predict this transformation.

This case of a 28-year-old male demonstrates one of the longest reported intervals—25 years—between the treatment of recurrent INSS Stage 3 neuroblastoma and the subsequent diagnosis of pelvic GN (Table 1), with

Table 1. Overview of present and previous published cases.

Case Report	Age at NBL Dx	Treatment	Interval between NBL and GN diagnoses*	GN Location	Outcome
This Case	45 days old	Chemotherapy, Radiotherapy, Surgery	25 years (after treatment of recurrence)	Pelvis/sacrum	Stable, asymptomatic
Przkora et al. [9]	6 years old	None initially; later surgical resection	11 years	Presacral	Stable post-resection
Boulter et al. [16]	Childhood	Chemotherapy, Stem Cell Transplant, Radiotherapy	>20 years	Not specified	Recurrence with Ganglioneuromatous foci
Christein et al. [8]	5 months old	Chemotherapy, Radiotherapy, Surgery	~28 years	Pancreas Small Intestine Stomach	Stable, asymptomatic
Yao et al. [10]	Case 1: 12 months old Case 2: 15 months old	Case 1: Surgery Case 2: Surgery	Case 1: 6 years Case 2: 13 years	Case 1: Pelvis Case 2: Periaortic, Renal Hilum	Case 1: Stable, Asymptomatic Case 2: Stable, Asymptomatic

* Interval measured from the last confirmed neuroblastoma activity; in the present case, from the treatment of the recurrence at 3 years of age.

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multiple presentations over time.

Unlike Przkora et al.'s case, which was based on biochemical evidence without histological confirmation, our patient had definitive pathology confirming both the initial poorly differentiated neuroblastoma and the later mature ganglioneuroma [9]. The patient received aggressive multimodal treatment, including chemotherapy, radiotherapy, and surgery, contrasting with the more conservative or unspecified treatments in prior cases, as in the case provided by Christein et al. [8]. The stable, asymptomatic nature of the GN in our patient supports current recommendations for observation in similar benign lesions. However, the available information does not establish when the maturation, if related to the original neuroblastoma, occurred.

If the current lesion is related to the original neuroblastoma, this case may offer insights into the biology of ultra-late neuroblastoma maturation, suggesting that tumors arising in the sacral/pelvic region may be more likely to undergo delayed differentiation, possibly influenced by the local microenvironment. It also raises important questions about whether chemotherapy promotes tumor maturation or selects for differentiated cell populations, as well as the mechanisms that allow tumor cells to remain dormant for decades. Unlike Cases by Boulter et al. and Christein et al., which showed mixed histology at recurrence, our patient's lesion, if it represents maturation of the original tumor, showed no residual neuroblastic elements and may challenge assumptions about the irreversible malignant potential of neuroblastoma in long-term survivors [8, 16]. These findings may underscore the importance of lifelong surveillance in neuroblastoma patients and may highlight pelvic tumors as key subjects for further study of tumor maturation pathways.

CONCLUSION

Based on our experience and the existing literature, we recommend long-term follow-up for patients with a history of NBL. This could include annual MRI or CT scan of the primary tumor site post-treatment [17]along with MIBG Scintigraphy [18], Circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) in blood or other biofluids [19], etc. Any new neurological symptoms should prompt immediate investigation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL

The authors are accountable for all aspects of the work. They will ensure that any inquiries regarding the accuracy or integrity of any component of the work are appropriately investigated and resolved. All procedures conducted in this study adhered to the ethical standards established by the institutional and/or national research committee and the revised Helsinki Declaration (2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review if necessary.

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