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Malignant peripheral nerve-sheath tumor arising in a previously irradiated neuroblastoma: report of 2 cases and a review of the literature

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Abstract *Background*. Only ten cases of the rare occurrence of a malignant peripheral nerve-sheath tumor (MPNST) arising in a ganglioneuroma either de novo or at a site of previous irradiation have been reported.
Patients and methods. We present two children who at the age of 19 months and 6 months were diagnosed with a cervicothoracic ganglioneuroblastoma and a retroperitoneal neuroblastoma, respectively. They both received radiation therapy as part of the treatment of their disease.
Results. Following a 12-year interval, MPNST arose inside a benign ganglioneuroma in both patients. We illustrate the imaging findings in these two cases and review the cases reported in the literature to increase awareness of this association among radiologists.

Introduction

Ten cases of the rare occurence of a malignant peripheral nerve-sheath tumor (MPNST) arising in a ganglioneuroma either de novo or at a site of irradiation have been previously reported [1–9] (Table 1). Only three of these cases have presented during the pediatric age range, and none of these has been illustrated in the radiologic literature. We present two new children with this unusual neoplastic association.

Case reports

Case 1

This girl presented at 19 months of age with a left cervicothoracic mass, which on biopsy proved to be a ganglioneuroblastoma. The patient received radiation therapy for a total of 2,700 cGy and was subsequently treated with chemotherapy, but this had no effect on tumor size. The mass was considered unresectable due to the involvement of the brachial plexus and vessels.

The patient remained asymptomatic with no change in the size of the mass on routine chest radiographs (Fig. 1 a). When she was 13.5 years old, she started losing weight and complained of Raynaud phenomenon in the left hand. Six months later a new 2 × 2-cm

Table 1 Previous reports of coexistent malignant peripheral nerve sheath tumor (MPNST) and ganglioneuroma

Previous reports	Sex	Age (years)	Site of presentation of MPNST + ganglioneuroma	Previous history	Outcome
Drago et al. (1997) [1]	Female	11	Left paraspinal region in thorax	No previous irradiation	27 months free of disease, after surgery, chemotherapy and radiation therapy
Grippari et al. (1996) [2]	Male	21	Posterior mediastinum	No previous irradiation	12 months free of disease after surgery and radiation therapy
Ghali et al. (1992) [3]	Male	27	Retroperitoneum	No previous irradiation	Recurred 16 months after surgery, treated with surgery and chemotherapy. Patient died with local recurrence and pleural metastases 8 months later
Damiani et al. (1991) [4]	Female	18	Retroperitoneum	No previous irradiation	4 years free of disease after surgery
Banks et al. (1989) [5]	Male	15	Paratesticular region + retroperitoneal lymphadenopathy	No previous irradiation	3 years free of disease after surgery and chemotherapy
Fletcher et al. (1988) [6]	Female	23	Left paraspinal region in thorax	No previous irradiation	14 months free of disease after surgery and radiation therapy
Chandrasoma et al. (1986) [7]	Male	30	Left adrenal	No previous irradiation HIV (+)	Recurred 4 months after surgery. Five months after new surgery, chemotherapy and radiation therapy presented with thoracic vertebral and paraspinal metastases. Patient died 3 months later
Keller et al. (1984) [8]	Female	20	Retroperitoneum + right psoas muscle	Abdominal neuroblastoma irradiated at age 14 months	Recurred in right psoas muscle 6 months after surgery and radiation therapy. Subsequently on chemotherapy
Ricci et al. (1984) [9]	Female	18	Left adrenal + left ovary	Retroperitoneal neuroblastoma irradiated at age 12 months	Lung metastases 14 months after surgery, treated with chemotherapy. Abdominal disemination 6 months later. Patient died 11 months later
Ricci et al. (1984) [9]	Male	10	Supranasal region	Left adrenal ganglioneuroblastoma irradiated and treated with chemotherapy at age 20 months. Frontal ganglioneuroma irradiated at age 22 months	Incomplete resection. Patient died 11 months later from progressive intracranial disease, electrolyte imbalances and pulmonary edema

left axillary mass was discovered. Computed tomography (CT) showed a large left cervicothoracic mass, of inhomogeneous attenuation with moderate amount of calcifications, extending from the level of the pyriform fossa down to the level of the aortic arch (Fig. 1 b,c). The trachea was displaced towards the right and compressed by the mass. The tumor also caused anterior displacement of the left carotid and jugular vessels and extended into the left C6–7 intervertebral foramen. Large left axillary nodes were also present, and in the thorax there was left pleural thickening, as well as two small densities in the periphery of the left lung posteriorly, suspicious for metastatic deposits. An angiogram depicted displacement of the left common carotid artery anteriorly and to the right, significant narrowing and inferior displacement of the left subclavian artery, and occlusion of the left vertebral artery. Myelogram was normal.

Surgery was then performed based on the signs of neurovascular compromise suggestive of progression of disease. Resection of the left cervicothoracic mass, left axillary dissection and biopsy of the left lung were performed.

Microscopy of sections from the main tumor mass revealed a very cellular spindle-cell sarcoma intermixed with ganglioneuromatous tissue. The sarcoma was present in one-third of the sampled tissue. No neuroblastoma was identified. The sarcomatous tissue had a primarily herringbone pattern of growth with enlarged clusters of atypical ganglion cells and extended to the capsular margins of the tumor mass. The sarcoma was anaplastic in nature

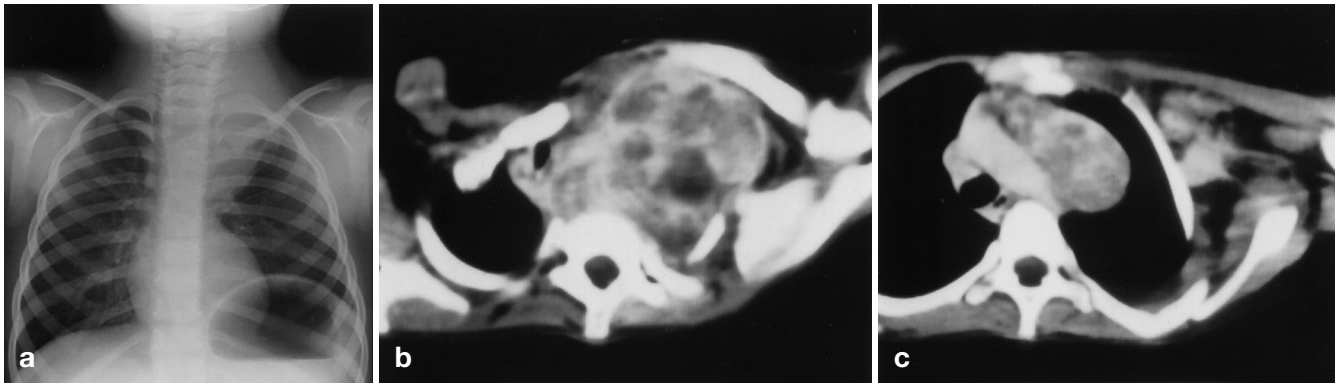

Fig. 1a–c Case 1. **a** AP chest radiograph at 4 years of age. Large left cervicothoracic ganglioneuroblastoma causes displacement of the trachea towards the right. There is associated elevation of the left hemidiaphragm due to involvement of the left phrenic nerve. **b, c** Enhanced CT scan through upper thorax at 14 years of age. Large left cervicothoracic mass of heterogeneous attenuation as a result of development of a malignant peripheral nerve-sheath tumor in a ganglioneuroma. The mass crosses midline and causes narrowing and marked deviation of the trachea towards the right (**a**). It extends inferiorly to the level of the aortic arch and left axillary lymphadenopathy is also noted (**b**)

with marked nuclear pleomorphism and atypical mitotic figures. Immunoperoxidase studies for several antigens were only positive for S100, which stained the spindle-cell element of the sarcoma. In addition, the neuron-specific enolase stain stained the ganglion cells within the neoplasm, as well as those within the ganglioneuroma positively. The histopathologic features of the sarcoma arising within this ganglioneuroma were those of a MPNST.

Following surgery, the patient received several cycles of chemotherapy, which were unsuccessful as the patient developed progressive metastatic disease and died 22 months after the diagnosis of MPNST had been made.

Case 2

This girl presented at 6 months of age with a midline retroperitoneal mass. Biopsy revealed the presence of a neuroblastoma (Fig. 2a). The patient received chemotherapy and radiation therapy (1,600 cGy).

Approximately 6 months later a second-look laparotomy was performed. At this time biopsy was done without any attempt of further resection due to the encasement of major vessels including the celiac axis. This biopsy showed a ganglioneuroblastoma.

The patient was followed regularly with annual sonography and one CT at age 8 (Fig 3a). These imaging studies did not show any change in the retroperitoneal mass.

At age 13, abdominal CT revealed changes in size and in the appearance of the anterior aspect of the retroperitoneal mass (Fig 3b) that had been stable for more than 10 years. At that time the significance of these findings was not fully appreciated. Fourteen months later, CT demonstrated further increase in size of the anterior part of the lesion (Fig. 3c). A laparotomy was then performed, but only a small biopsy sample was obtained due to excessive bleeding. The histology was now erroneously interpreted as an embryonal rhabdomyosarcoma. Additional chemotherapy (sarcoma protocol) did not provide any response.

Resection of the retroperitoneal mass was performed 11 months later. The specimen showed the presence of a high-grade sarcoma with features of MPNST (Fig. 2b) arising in a ganglioneuroma. Part of the cystic changes noted on the abdominal CT represented marked dilatation of pancreatic ducts, which were entrapped within the tumor; other areas of the adjacent pancreas showed fibrosis with entrapped residual endocrine islets. The patient was then managed conservatively and died 3 months after the last surgery.

Discussion

The maturation of a neuroblastoma, either spontaneous or induced by radiation therapy, into more differentiated ganglioneuroblastoma and ganglioneuroma is well recognized [1, 3]. Many authors believe that all ganglioneuromas are the result of the evolution of a previous neuroblastoma or ganglioneuroblastoma [1, 3]; this is however debatable since most ganglioneuromas are isolated, have a different distribution than childhood neuroblastomas, and are found in patients with no previous history of neuroblastoma [1, 3, 7]. Patients with unresectable or partially excised ganglioneuroma, in whom there is a history of previous ganglioneuroblastoma or neuroblastoma, are routinely followed up clinically and with imaging studies to detect recurrence of foci of neuroblastoma.

MPNST are rare tumors that may be associated with neurofibromatosis type 1 (50%) or previous irradiation (10%) [10]. We are unaware of chemotherapy being a predisposing factor for the development of this second malignancy. The association of MPNST with ganglioneuroma is extremely uncommon, and its histogenesis is not well understood [1]. In our review of the literature, in addition to two cases briefly alluded to by Enzinger and Weiss [11], we found only ten well-described cases of the coexistence of these two neoplasms [1–9], and of these, only three presented at a pediatric age [1, 5, 9] (Table 1).

Our two patients and three others published in the literature have a history of irradiation of a neuroblastoma or ganglioneuroblastoma 8–19 years prior to the

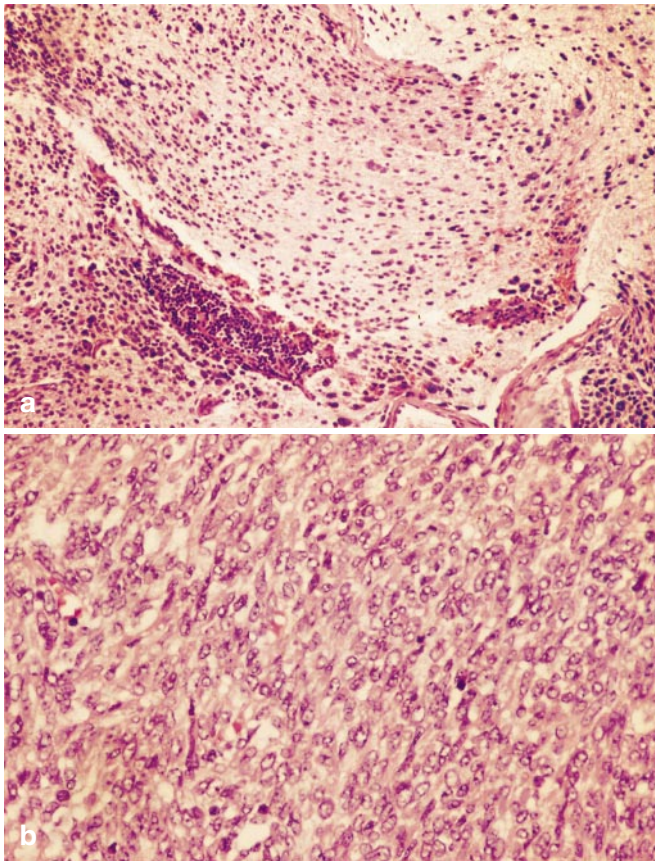

Fig. 2a, b Case 2. **a** Biopsy of retroperitoneal lymph node at age 6 months. The node is infiltrated by small cells with hyperchromatic rounded nuclei and with thin cytoplasmic processes giving a pattern of fibrillary background. The features are diagnostic of neuroblastoma (H&E). **b** Histological sample of the resected retroperitoneal mass shows dense proliferation of medium-sized spindle and oval cells with clear nuclei and light eosinophilic cytoplasm (H&E) consistent with MPNST

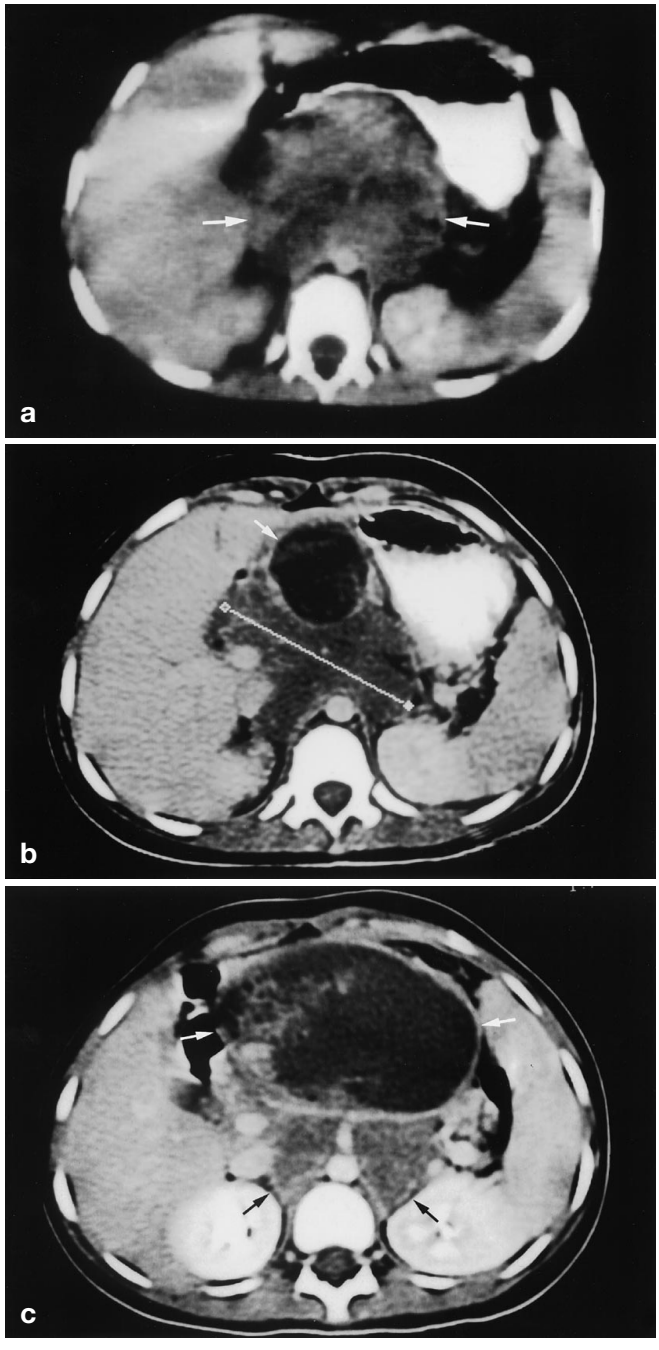

Fig. 3a–c Case 2. Enhanced CT scans through upper abdomen at ages 8, 13, and 14. **a** Age 8. Heterogeneous retroperitoneal ganglioneuroblastoma anterior to the aorta (*arrows*) that causes anterior displacement of the pancreas and stomach. The mass had remained stable on sonography for more than 7 years. **b** Age 13. Interval increase in size of the retroperitoneal mass (*cursors*) due to the development of a malignant peripheral nerve-sheath tumor. Note the rounded low-attenuated area anteriorly within the mass (*arrow*). **c** Age 14. Further increase in size of the retroperitoneal mass, particularly of the low-attenuated anterior component (*white arrows*), which on pathology proved to be due to tumoral necrosis and dilated entrapped pancreatic ducts

presentation of the MPNST [8, 9]. Four of these cases, including our case 1, originally presented between 1953 and 1971 when routine follow-up with sonography or CT was not available or not considered. In these four cases, the investigation was prompted by the development of symptoms related to the growth of the mass. The remaining patient, our case 2, is an exception, as she first presented in 1981 and was routinely followed up with these imaging modalities, and in whom CT demonstrated a change in the size and attenuation of the lesion before symptoms appeared.

Of the seven patients in whom the MPNST arose spontaneously in a ganglioneuroma, six presented with symptoms related to local mass effect at the time of diagnosis; the other case was found incidentally on a chest radiograph [2].

Radin et al. [12] have described the imaging appearances of abdominal ganglioneuromas. On sonography,

they appear as homogeneous solid masses with echogenicity similar to the hepatic or splenic parenchyma. On CT, ganglioneuromas are usually homogeneous with attenuation less than that of muscle and small calcifications may be present. In larger tumors, heterogeneity can be seen on the enhanced CT images as in our case 2 (Fig. 3 a). The imaging appearances of ganglioneuromas remain stable with time. When MPNST arises in a ganglioneuroma, there is an increase in size and a change in the texture of the mass, as in our case 2, which showed the development of a large area of fluid attenuation in the anterior aspect of the mass, which was due to necrosis and dilated pancreatic ducts (Fig. 3 b,c). These nonspecific CT features of MPNST, coexisting with ganglioneuromas described as large oval masses of heterogeneous attenuation, with areas that enhance to a greater extent or equal to the liver and cystic areas, have been previously reported in two adults [7, 12]. However, our case is the first one to illustrate the evolution from pure ganglioneuroma to ganglioneuroma mixed with MPNST.

Two of the cases in the literature [1, 2] have been evaluated with magnetic resonance imaging, but only one is well described [1]. In that case the mass appeared of intermediate signal intensity on T1-weighted images and showed marked and heterogeneous enhancement following the injection of intravenous gadolinium.

The outcome of patients with this rare association of MPNST and ganglioneuroma is very poor, particularly when there is a history of previously irradiated ganglioneuroblastoma or neuroblastoma. All five patients with this history have not responded well to therapy and four of them, including our two, have died. In the remaining seven patients, with de novo development of MPNST, five persist free of disease (1 year to 4 years) following therapy (surgery, chemotherapy, radiation therapy or a combination of them), and two have died following rapid relapse with metastatic dissemination [3, 7, 12].

In summary, the routine clinical and imaging follow-up of patients with ganglioneuroma, especially those with a prior history of irradiated neuroblastoma, is mandatory, not only because of the risk of recurrence of neuroblastoma, but also to detect the development of a second malignancy, such as MPNST, which is associated with a poor outcome. The imaging findings of this neoplastic association are non-specific, as they may also be seen with tumor recurrence, but a change in the size or texture of these masses must alert the radiologist of the possible complication of the development of a second malignancy.

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