CORRESPONDENCE

Synchronous occurrence of neuroblastoma tumour and exocrine carcinoma of the pancreas in a child

To the Editor,

Neuroblastomas are the most common extracranial solid tumours of childhood and the most common tumours in the first year of life. While they account for 8—10% of all paediatric cancers, they result in about 9% of childhood deaths.1

Paediatric pancreatic tumours are an extremely rare and heterogeneous group of tumours with little epidemiological data available. They represent 0.2% of paediatric cancers. The estimated incidence is 1—2 cases/10 million children or young adults in the United States.2

Despite considerable progress in treatment, neuroblastoma survivors are at high-risk of developing second malignant neoplasms (SMN), mainly haematopoietic malignancies. A 2-year-old girl presented with stage 4 thoracoabdominal bulky neuroblastoma and increased urinary catecholamines. MIBG scan revealed fixation at the primary tumour site, bone metastases and bone marrow. Diagnosis was performed on trephine biopsies showing bilateral infiltration by a stroma-poor neuroblastoma tumour according to the criteria of INPC.3 No N-MYC or ALK amplification was identified.

First line chemotherapy, including two courses of vincristine-cyclophosphamide-doxorubicine and two courses of etoposide-cisplatin, induced partial MIBG response but the primary remained unresectable. Two additional courses of etoposide-cisplatin were ineffective. Bone marrow aspirates and trephine biopsies were negative. Two cycles of topotecan and 131 I-MIBG therapy were added.

Eighteen months after diagnosis, partial resection was performed. Histological examination after chemotherapy showed a predominant schwannian stroma-rich neuroblastoma tumour with prominent schwannian component and mature ganglion cells associated with foci of schwannian stroma-poor neuroblastoma and lymph node metastasis. Treatment was completed by high dose chemotherapy (busulfan-melphalan) and autologous stem cell rescue, followed by 1 year of maintenance therapy with retinoic acid.

At age 14, exudative enteropathy appeared secondary to lymphatic compression. Debulking surgery was performed on the sub-mesocolic component and the supraceliac component was intentionally left in place due to the surgical difficulties. The tumour had the same histological appearance 12 years after the original diagnosis and treatment. Of note, normal pancreatic acini were entrapped within the tumour at that time.

Three years later, a complementary resection of the supraceliac part of the tumour was performed and the tumour was found to be adherent to the pancreas.

The specimen, measuring 11 × 10 × 4.5 cm and weighing 177 g, had a multinodular and myxoid appearance with necrotic changes and was surrounded by a rim of pancreatic parenchyma.

Microscopic examination demonstrated a ganglioneuroblastomatous component admixed with myxoid matrix, containing cohesive epithelial atypical cells exhibiting glandular differentiation with large areas of tumour necrosis (Fig. 1 and 2). Perineural invasion was observed within this epithelial component. Rare residual pancreatic ducts and numerous Langerhans islets were entrapped within the tumour without pancreatic intraepithelial neoplasia. Neoplastic cells strongly expressed pan-cytokeratin (CKAE) and focally CK7. The proliferative index was high (60%). Neuroendocrine markers were all negative, as were BCL10, PHOX2B, WT1, and ALK. P53 was weakly expressed by occasional tumoural cells. MMR protein expression was retained in both the neuroblastotic and epithelial components. The final diagnosis was colliding neuroblastoma tumour and pancreatic exocrine carcinoma.

Next generation sequencing mutation analysis further identified activating mutation in the exon 2 of KRAS gene and the TK domain of BRAF gene.

Soon after surgery, the patient developed hepatic metastases of the pancreatic exocrine carcinoma, histologically documented. She died of tumour progression 20 months after the second tumour diagnosis, despite treatment including gemcitabine, MEK inhibitors, and 15 folotinix courses.

Neuroblastoma has remarkable heterogeneous behaviour ranging from spontaneous regression to progressive resistance to intensive therapy. Due to this heterogeneity, prognosticating outcome at diagnosis became necessary to allow optimal treatment. Four categories (very low, low, intermediate, and high risk) based on clinical and biological factors are defined in the International Neuroblastoma Risk Group (INRG) classification system.1

Undeniably, the last decades have seen a marked improvement in the outcome of children with neuroblastoma through modern risk-adapted treatment approaches along with molecular-targeted therapy, leading to an increased number of survivors4,6 and in parallel an increased risk of SMN, at least in high-risk patients.

Neuroblastoma survivor patients treated with previous modalities were at high risk of developing SMN with cumulative incidences of 3.6—10%. With modern therapeutic protocols, including chemotherapeutic regimens, radiation therapy, and myeloablative therapy with stem cell rescue, the risk of SMN malignancies remains increased, particularly in high-risk patients.7 Other potential treatment-related complications or late effects include endocrine, cardiovascular, sensory, pulmonary and renal complications.6

In a large study from the INRG Project, including 5987 patients treated according to risk-based therapeutic trials, 44 (0.72%) developed SMN. The median follow-up was 63 months, and the median age at SMN diagnosis was 6.7 years. The factors associated with increased risk of SMN were stage 4, unfavourable histology, and diagnosis before 2006. The most common SMN were haematopoietic malignancies (44%), seen in more than half of patients treated with high-risk disease. Carcinoma and brain tumours represented 14% each, and sarcoma 28%. The primary site of carcinoma in this series was not specified.7

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High-risk neuroblastoma survivors are at 17.5-fold risk of SMN, with a high prevalence of haematopoietic malignancies (AML) in high and intermediate-risk survivors within 5 years of the diagnosis of neuroblastoma. Interestingly, even in the group of low-risk patients predominantly treated with surgery alone, there was a higher risk of SMN, suggesting underlying genetic susceptibilities in neuroblastoma patients.

Secondary leukaemia has also been described in neuroblastoma patients treated with intensive chemotherapy associated with 131I-MIBG, as demonstrated in the following studies. In the series published by Feng et al., including 24 patients with high-risk stage 4 or MYCN-amplified neuroblastoma, one patient developed a haematological SMN. In two other studies including more than 200 neuroblastoma patients treated with I-131 MIBG, eight developed SMN, most of them leukaemias, and none pancreatic. Of note, rare cases of secondary renal cell carcinomas have been reported following neuroblastoma even in the absence of previous chemotherapy.

Neuroblastomas have been associated with various neoplasias in the context of genetic predisposition, including solid organ tumours and haematopoietic malignancies. Children with specific cancer predisposition syndromes are at increased risk of neuroblastomas and need surveillance recommendations. Cancer predisposition syndromes include PIK3CA-related segmental overgrowth, Rubinstein–Taybi, Simpson–Golabi–Behmel, Sotos, WAGR and Wolf–Hirschhorn syndromes. Familial neuroblastomas are related to PHOX2B and ALK susceptibility genes and represent 1–2% of cases. Similarly, pancreatic adenocarcinoma has been associated with Lynch syndrome.

An analysis of the SEER database between 1973 and 2006 found that 34 of 2823 patients with neuroblastoma or ganglioneuroblastoma developed a second malignancy. None of them were located in the pancreas.

Pancreatic tumours are uncommon in children, and the incidence of pancreatic malignancies is only 0.018/100,000 versus 12.6/100,000 in adults in the USA. They comprise a wide range of histologies, including solid papillary tumours (SPT), pancreatoblastomas, carcinomas (ductal and acinar), endocrine tumours, and sarcomas. Carcinomas are very uncommon compared to SPT and pancreatoblastomas, as highlighted by various series.

In a large multi-institutional study of 65 duodenopancreatectomies for pancreatic neoplasms in patients under 21 years old over a 27-year period, the median age at diagnosis was 13 years (range 4 months–21 years). The most common pathological diagnosis was SPT (52%), with a mean age of 14 years (range 8–19 years). Pancreatoblastomas were the most common malignant tumours in younger age group patients (12%) with a mean age of 10 years (range 4–18 years). Carcinomas represented only 8% of cases. Only two patients had underlying genetic predisposition consisting of Beckwith–Wiedman and Lynch syndromes.

In another series published by Perez et al., among 55 pancreatic tumours identified in children 19 years or younger, carcinomas (either acinar and ductal) represented 20% of cases, SPT and pancreatoblastomas 36%, endocrine tumours 35% and sarcomas 9%.

In the American National Cancer Database between 2004 and 2014, 109 children were identified with a pancreatic neoplasm. Adenocarcinomas represented 16%, SPT 30%, endocrine tumours 27% and pancreatoblastomas 16%. None of these tumours were second cancers.

Secondary pancreatic tumours have been reported in adults following therapy for other tumours such as Hodgkin lymphoma.

To conclude, to our best knowledge, pancreatic carcinoma NOS following neuroblastoma, as described here, has not yet been reported. This patient presenting with stage 4 neuroblastic tumour diagnosed before 2006 without MYCN amplification, developed a SMN 15 years after the initial diagnosis and multimodality treatment, including chemotherapy, iterative reduction surgeries and I-131 MIBG therapy. Whether chemotherapy alone, I-131 MIBG therapy alone, or the combination of both treatment modalities played a pivotal role in the occurrence of pancreatic carcinoma is difficult to affirm in this case report. The hypothesis that the pancreas, located close to the initial tumour targeted by the metabolic radiation therapy with I-131 MIBG, has received a significant dose of radiation deserves to be raised, as this pancreatic carcinoma could be a radiation-related second neoplasm. However, SMN is a multifactorial disease, and neuroblastoma patients have a genetic susceptibility to SMN, regardless of disease stage and treatment modality.
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