CASE REPORT

Coexistence of Peripheral Primitive Neuroectodermal Tumor and Tetralogy of Fallot

Chien-Chang Juan*, Giun-Yi Hung[1], Yann-Jang Chen[2], Pi-Chang Lee

Division of Pediatric Cardiology and [1]Division of Pediatric Hematology, Department of Pediatrics, Taipei Veterans General Hospital, and [2]National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

We describe a little girl with tetralogy of Fallot (TOF) who was found to have a huge peripheral primitive neuroectodermal tumor (pPNET) when she developed progressive difficulty in standing and crawling at the age of 11 months. The tumor was located in the left paraspinal region (T4–T12), with intraspinal extension causing severe compression. Nine days after surgical decompression with laminectomy, chemotherapy was initiated with alternative courses of vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide every 3 weeks. The muscle power in her legs recovered substantially after 2 courses of chemotherapy. Although peripheral blood for cytogenetic study revealed no chromosome abnormality, recent cytogenetic analysis has revealed a high frequency of reciprocal translocation t(11;22)(q24;q12) detected in pPNET and a strong association between TOF and chromosome 22q11 microdeletion (del 22q11). Both genetic defects involve chromosome 22q in the close region. This case report illustrates the necessity of investigating for cytogenetic change in chromosome 22 and close follow-up due to the possibility of subsequent development of malignancies in patients with TOF. [*J Chin Med Assoc* 2006;69(3):134–137]

Key Words: chromosome 22, primitive neuroectodermal tumor, tetralogy of Fallot

Introduction

Primitive neuroectodermal tumor (PNET) and tetralogy of Fallot (TOF) have never been reported to coexist in 1 patient, although the tendency of developing malignancy in patients with congenital defects has been well documented.[1] Extracranial PNET is a small, round-cell malignancy of presumed neural crest origin arising outside the central and sympathetic nervous system, called peripheral PNET (pPNET). It predominantly affects children and adolescents, presenting a highly malignant clinical behavior. Recent developments in cytogenetic analysis have revealed a high frequency (up to 95%) of reciprocal translocation t(11;22)(q24;q12) detected in pPNET,[2,3] and a strong association between TOF and chromosome 22q11 microdeletion (del 22q11).[4] As both of the genetic defects involve chromosome 22q in the close region, it is interesting for the pediatrician to investigate if both pPNET and TOF could occur concurrently in the same patient.

Case Report

In October 2004, an 11-month-old girl was admitted to the pediatric ward of Taipei Veterans General Hospital with the chief complaint of progressive lower limb weakness in the past week. The patient was found by her mother to have difficulty in standing and crawling for 2 days. The infant had TOF, which had been diagnosed after birth. In May 2004, because of

*Correspondence to: Dr. Chien-Chang Juan, Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: ju651125@yahoo.com.tw • Received: May 13, 2005 • Accepted: September 14, 2005

moderate pulmonary stenosis (PS) and frequent cyanotic spells, she had received cardiac catheterization and balloon valvular dilatation for PS, and beta-blocker (propranolol) had also been prescribed, after which she was in a relatively stable condition and followed-up regularly in the pediatric cardiology ward.

On this admission, physical examination revealed decreased deep tendon reflex and muscle power in the lower extremities. T-spine myelopathy was suggested. Chest X-ray showed a mass shadow over the cardiac region (Figure 1). Whole-spine magnetic resonance imaging (MRI) revealed a large contrast-enhanced tumor mass over the left paraspinal region (T4–T12), with intraspinal extension causing severe compression (Figure 2). Tumor markers, including α-fetoprotein, β-homologous chorionic gonadotropin, urine vanillylmandelic acid and urine catecholamine, were within normal limits. Lactate dehydrogenase 315 U/L and neuron-specific enolase 14.52 ng/mL were found.

For spinal decompression, emergency laminectomy (from T5 to T9) and tumor biopsy were performed on the third day of admission (October 6, 2004). Hypervascular and reddish tumor masses in the epidural space over T5–T9 were found. Pathology reported a small round-cell tumor with mild nuclear pleomorphism, scant eosinophilic cytoplasm and a fibrillary stroma (Figure 3). These cells were weakly reactive for epithelial membrane antigen, and nonreactive for glial fibrillary acidic protein. The MIB-1 (a monoclonal antibody that detects cell-cycle–associated Ki-67 antigen) labeling index was 30%. The tumor was consistent with PNET. Peripheral blood was taken for routine chromosome banding studies and specialized interphase fluorescent *in situ* hybridization studies for mapping to 22q11. However, no chromosome abnormality was found.

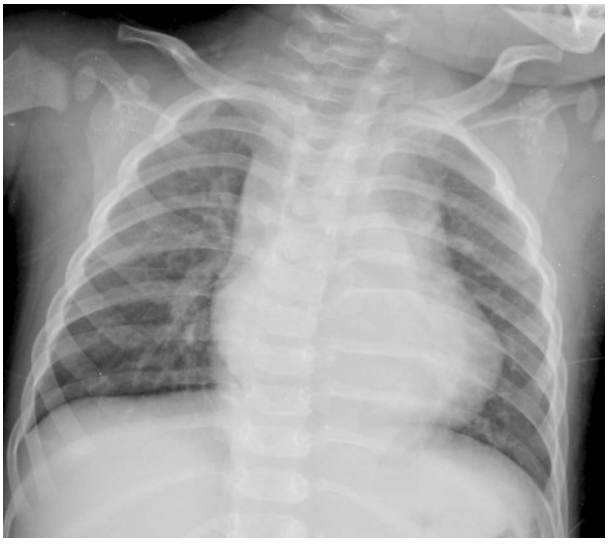

Figure 1. Chest X-ray shows significantly widened upper mediastinum with a mass shadow over the cardiac region.

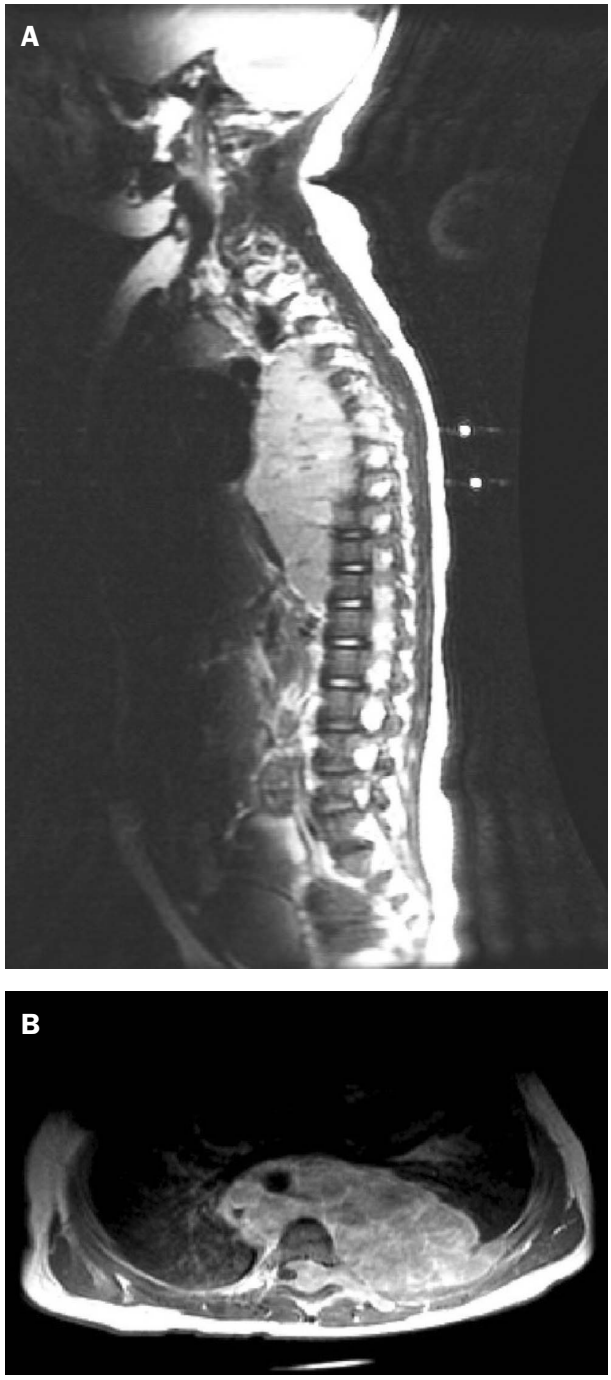

Figure 2. (A) Whole-spine magnetic resonance imaging shows the presence of a large paraspinal soft tissue mass (T4–T12; 10 × 7 × 3.5 cm in size). (B) The soft tissue mass with intraspinal extension causes severe compression of the spinal cord around the T7–T8 level.

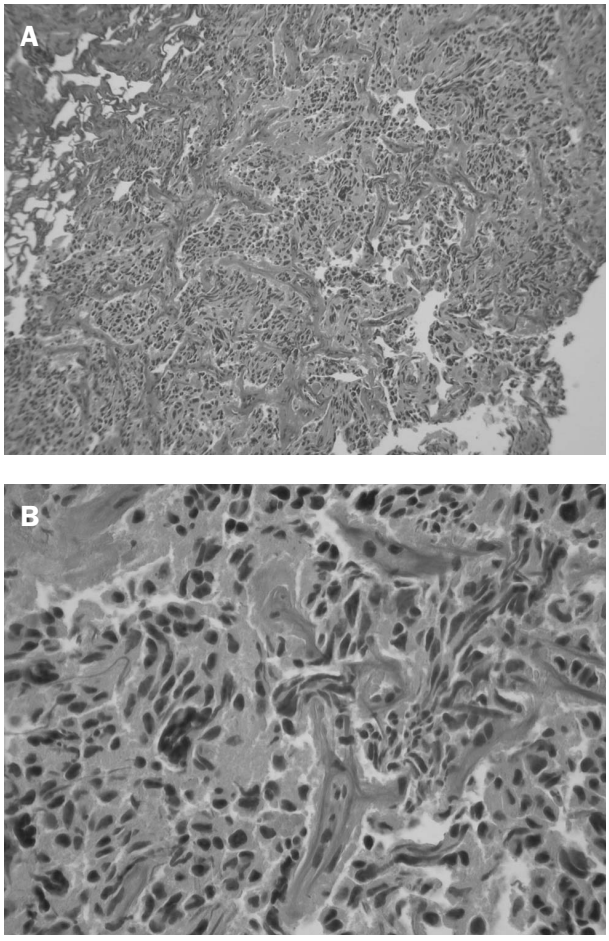

Figure 3. Photomicrography (A, × 100; B, × 400) shows small cells with mild nuclear pleomorphism, scant eosinophilic cytoplasm, and a fibrillary stroma (hematoxylin & eosin, × 100 and × 400, respectively). These cells are weakly reactive for epithelial membrane antigen, but nonreactive for glial fibrillary acidic protein. MIB-1 (a monoclonal antibody that detects cell-cycle-associated Ki-67 antigen) labeling index is 30%.

Nine days after surgery, chemotherapy was initiated with alternative courses of VDC (vincristine, 1.5 mg/m^2 on day 1; doxorubicin, 37.5 mg/m^2/day on days 1–2; cyclophosphamide, 1.2 g/m^2 on day 1) and IE (ifosfamide, 1.8 g/m^2/day on days 1–5; etoposide, 100 mg/m^2/day on days 1–5) every 3 weeks. The muscle power in her lower limbs recovered substantially after the second course of chemotherapy, and she could stand up after the fourth course of chemotherapy. Delayed surgical excision was planned due to bulky tumor at difficult sites. However, at the pancytopenic stage after completion of the fifth course of chemotherapy, the infant suffered from a neutropenic fever, which proceeded to septic shock, resulting in death.

Discussion

PNET within the spinal column may be of the central or peripheral type in intramedullary, intradural-extramedullary, or epidural presentation. Deme et al[5] reviewed 13 cases of intramedullary or intradural PNET, and concluded that these neoplasms frequently disseminate via the cerebrospinal fluid, rarely metastasize outside the central nervous system, and appear more commonly in adults than in children. On the other hand, pPNET located within the epidural space, as in our case, is very rare and was first reported by Angervall and Enzinger in 1975.[6] Up to the present, only 3 cases of pPNET within the spinal epidural space have been reported.

pPNET has the clinical features of aggressive growth and rapid progression with distant metastasis to bone, liver and lung, which differs from the central type. Furthermore, it can be distinguished from the central type of PNET and other small blue-cell tumors by the characteristic translocation t(11;22)(q24;q12).[7,8] In our patient, chromosome analysis of the tumor was not performed because she died before debulking surgery, and the surgeon was not able to send a specimen for further cytogenetic study at the initial biopsy. We could only make the diagnosis of pPNET according to the location of the tumor (epidural) and the pathologic report.

In the English literature, the most common symptoms in patients with pPNET in the spinal column include back and/or radicular pain and leg paresis (91.3% of cases), and bladder and bowel dysfunction, suggesting that the signs and symptoms resulted from compression of the spinal cord, cauda equine, and nerve root. As our patient could not express her feeling of pain, the sign of spinal compression was not detected until leg paresis appeared. In this situation, consultation with a pediatric neurologist, neurosurgeon and oncologist is critical for determining the best course of emergency management. If lymphoma is highly suspected, steroids should be administered instead of surgical decompression. Contrast-enhanced spinal MRI to examine the extent of involvement should be arranged immediately, and histopathologic examinations, together with cytogenetic analysis, are necessary at tumor biopsy to delineate the tumor and confirm the diagnosis.

Frequently, laminectomy with tumor resection is indicated for the relief of neurologic symptoms. In the literature,[9] 72.7% of tumors were only partially resected and resulted from infiltration of surrounding tissues, as in our patient, and they seemed to have a high incidence of local recurrence and high mortality.[10]

Besides surgical resection, radiotherapy and chemotherapy form an important adjuvant therapy for PNET.[11,12] The reported doses of radiotherapy suggested for patients with PNET in the spinal canal varied between 30.6 and 56 Gy,[10] and it is especially essential in patients with incomplete resection of the primary tumor. Since our patient was young and responded well to chemotherapy, radiotherapy was only considered as adjuvant therapy for local control.

For patients with pPNET, the most common chemotherapeutic agents used are vincristine, adriamycin, cyclophosphamide, ifosfamide and actimomycin-D. Some investigators have reported the positive impact of high-dose chemotherapy followed by peripheral blood stem cell transplantation on clinical outcome,[13–15] but others have reported failure in improving overall survival rates and the increasing incidence of secondary malignancy. Even with radiotherapy plus chemotherapy, spinal PNET is reported to have a poor prognosis, with the 5-year survival rate ranging from 0% to 37.5%.[9]

In recent cytogenetic studies, the chromosomal translocation of t(11;22)(q24;q12) was found to be highly specific to pPNET, and may result in the formation of a chimeric gene, *EWS/Fli-1*.[16] It was reported to act as an alternative transcription factor to promote the oncogenesis of PNET. Serial reports showed that the abnormal chromosome 22 may play an important role in the development of neoplasms, including epithelioid sarcoma, insulinoma, malignant meningiomas, follicular thyroid carcinoma, and malignant rhabdoid tumor. Chromosome 22q11 microdeletion (del 22q11) is implicated in a number of constructional heart defects, especially in TOF. Recently, it has also been reported to be associated with the diverse abnormalities classified under the acronym CATCH 22. Therefore, abnormalities of chromosome 22 seem to play a role in the development of congenital heart defects and the oncogenesis of neoplasm. This 11-month-old girl not only suffered from TOF but also pPNET around the spinal column. We tried to find out the cytogenetic features of TOF and pPNET in this patient, but no chromosome abnormality was found from her peripheral blood specimen.

In conclusion, pPNET rarely originates from the spinal column, and the prognosis is poor. The initial presentation in infancy might be leg weakness that can be easily neglected by parents. Tumor size, extent of disease, and complete surgical resection may influence the overall survival rate and incidence of local recurrence. Surgical resection combined with multiagent chemotherapy or radiotherapy is recommended.

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