Peripheral Primitive Neuroectodermal Tumor of the Chest Wall of a 69-year-old Man


Abstract

We report a case of peripheral primitive neuroectodermal tumor (pPNET), which belongs to the pPNET/Ewing’s sarcoma family, arising in the chest wall of a 69-year-old man. He had high levels of serum neuron-specific enolase and pro-gastrin-releasing peptide, which are believed to be useful diagnostic blood markers for small cell lung carcinoma (SCLC). Microscopically, the tumor was composed of solid nests and sheets of monotonous, primitive, small round cells with a few rosettes, making it difficult to distinguish from SCLC. Immunohistochemically, the tumor cells showed intense cell membranous immunoreactivity for MIC2 protein (CD99). EWS/FLI-1 chimeric mRNA that originated from the characteristic t(11;22)(q24;q12) chromosomal translocation was detected by RT-PCR and nucleotide sequence analysis. These results confirmed the diagnostic validity of the present tumor being a pPNET, thus raising the possibility that in the past, pPNETs which have arisen in the chest have been mistakenly diagnosed as SCLC.

Key words: MIC2, neuron-specific enolase, pro-gastrin releasing peptide, Ewing’s sarcoma, EWS/FLI-1 chimeric mRNA, pPNET

Introduction

Peripheral primitive neuroectodermal tumor (pPNET), i.e., peripheral neuroepithelioma, is a small-round cell tumor of putative neuroectoderm origin, and is the second most common sarcoma among children and young adults (1, 2). It may occur anywhere in the body and within any age group; however, it is most likely to occur in the bone and soft tissues. pPNETs may contain well-formed rosettes or pseudorosettes; however, these features are not essential for such a diagnosis (2). Cases where rosettes are absent or poorly formed overlap with Ewing’s sarcoma and malignant small cell tumor of the thoracopulmonary region (Askin tumor), sharing a common reciprocal translocation of the long arm of chromosomes 11 and 22, t(11;22)(q24;q12), in greater than 87% of cases (pPNET/Ewing’s sarcoma family) (3–5). Recently developed reverse transcription-polymerase chain reaction (RT-PCR) has facilitated the detection of EWS/FLI-1 chimeric transcripts originating from the characteristic t(11;22)(q24;q12) translocation of pPNET/Ewing’s sarcoma family (3, 6, 7). In addition, immunohistochemical positivity of MIC2 protein (CD99) is also considered to be of diagnostic help in cases in which the tumor is of the pPNET/Ewing’s sarcoma family (2, 8, 9). However, MIC2 protein expression is observed in a small number of small cell lung carcinoma (SCLC) (10).

Askin tumor rarely occurs in elderly persons and some cases of Askin tumor have been reported to have high levels of serum neuron-specific enolase (NSE) (11, 12), which is believed to be a useful blood tumor marker for SCLC (13, 14). We describe a case of pPNET of the chest wall in a 69-year-old man who had high levels of serum NSE and progastrin releasing peptide (proGRP); the diagnosis of pPNET was confirmed by MIC2 protein immunostaining, and RT-PCR and nucleotide sequence analysis for EWS/FLI-1 chimeric mRNA.

Case Report

A 69-year-old man who had been treated for angina pec-
Toriz was referred to our hospital because of an abnormal shadow on his chest roentgenogram. He had medical history of radical prostectomy; the pathologic analysis of the prostate tumor resected last year showed moderately differentiated adenocarcinoma without lymphatic metastasis. Physical examinations showed no abnormal findings. Laboratory findings disclosed mild normocytic anemia. Serum levels of NSE (17.4 ng/ml, normal range: 0–10.0 ng/ml), and proGRP (754 pg/ml, normal range: 0–46 pg/ml) were elevated. A chest roentgenogram on admission showed a mass with extrapleural sign on the left upper lung. Chest computed tomography (CT) demonstrated the tumor (7.0 cm×2.5 cm) adjacent to the pleura with markedly swollen mediastinal lymph nodes (Fig. 1). Magnetic resonance imaging of the brain, abdominal CT, and bone scintigraphy demonstrated no evidence of distant metastasis. Percutaneous needle biopsy was done, and pathological findings disclosed small round cell proliferation and immunostaining proved the expression of MIC2 protein. Chemotherapy was done using cisplatinum and etoposide without any response. The patient rapidly deteriorated and expired due to tumor growth and respiratory failure.

Autopsy was done and it was releaved that the tumor arose in the left chest wall with direct invasion to the left lung, pericardium and diaphragm. Mediastinal lymph nodes were markedly swollen.

Histopathological exmination showed small round cell proliferation (Fig. 2A). The small round tumor cells were immunohistochemically positive for MIC2 (clone 12E7, Dako Japan, Kyoto, Japan; Fig. 2B), S-100, NSE and proGRP, and negative for MyoD1 and desmin. To detect EWS/FLI-1 chimeric mRNA, RT-PCR analysis was performed. Total RNA was isolated from fresh frozen tumor tissue by a modified guanidine isothiocyanate method with Trizol (Gibco/BRL, Gaithersburg, MD), and was reverse-transcribed to complementary DNA (cDNA) with an oligo(dT)16 or a random hexamer (Perkin-Elmer, Foster City, CA) using Omniscrypt reverse transcriptase kit (Qiagen K.K., Tokyo, Japan). The successful reverse transcription was controlled by amplifying a β-actin fragment. To amplifying the putative EWS/FLI-1 cDNA, PCR was performed with the primers originally described by Zucman et al (7), for 11.3, 5’-ACTCCCCGTGGGCCCTCC-3’ and 22.8, 5’-CTAGTTACCCACCCAAA-3’. A hot-start, 30-cycle PCR was done under the following conditions: denaturation for 45 seconds at 95°C, annealing for 1 second at 55°C, elongation for 1 second at 70°C. The amplified cDNA was identified by 2% agarose gel electrophoresis and ethidium bromide staining. A single approximately 579 base-pair cDNA product was detected with ethidium bromide staining (data not shown). The band was considered to correspond to the
Figure 3. Schematic and nucleotide sequence showing EWS/FLI-1 fusion genes. RT-PCR employing EWS/FLI-1 primers was used to amplify chimeric fusions. Sequence analysis depicts a frame fusion between EWS and FLI-1.

EWS/FLI-1 fusion transcript, type 1 (7). Sequencing primers were used for 22.3, 5′-TCCTACAGCCAAGCTCCAAGTC-3′ and 11.11, 5′-TGTTGGGCTTGCTTTTCCGCTC-3′ (7). RT-PCR amplified products were subcloned and sequenced. Nucleotide sequence analysis demonstrated a frame fusion between EWS and FLI-1 (Fig. 3). EWS/FLI-1 chimeric mRNA that originated from the characteristic t(11;22) (q24;q12) chromosomal translocation was detected by RT-PCR and nucleotide sequence analysis.

Discussion

pPNETs are described in the context of malignant tumor of the peripheral nerve of children and young adults (1, 2). Histologically, pPNETs are characteristic by the presence of small round cells arranged in a lobular pattern and associated with rosettes or pseudorosettes (2). Immunohistochemical profile of pPNETs varies depending on the studies (2). Most agree that the tumors strongly express NSE and MIC2 protein, which is the cell antigen (p30/32) encoded by the MIC2 gene (2, 8, 9). Leu-7, synaptophysin, S-100 protein, neurofilament protein and chromogranin are variably positive within these tumors, but glial fibrillary acidic protein is consistently negative (2). MIC2 protein is highly characteristic but not totally specific for neuroepithelioma and Ewing’s sarcoma, since it may also be identified in some lymphomas and rhabdomyosarcomas (2). In addition, expression of MIC2 protein has been observed in a small number of SCLC (10).

Ewing’s sarcoma and pPNET related with solid tumors of childhood, in greater than 87% of cases, show cytogenetic evidence of a translocation between chromosomes 11 and 22 (3–5). As a consequence of this translocation, the 5′ portion of the EWS gene from band 22q12 is fused to the 3′ portion of the FLI-1 gene from band 11q24 (3–5). This translocation, resulting in the formation of chimeric transcripts, formed the basis of a sensitive and specific diagnostic assay for the pPNET/Ewing’s sarcoma family.

NSE and proGRP are believed to be diagnostic blood tumor markers for SCLC (13, 14). However, NSE has frequently been expressed in pPNETs (2) and in some cases of pPNETs elevated levels of serum NSE have been reported (11, 12). In addition, Mikami et al (15) reported a case of pPNET which was negative for proGRP in both serum and tumor cells.

To our knowledge, there has been no report to document elevation of serum Pro-GRP in a patient with pPNET which was confirmed by MIC2 immunostaining, and RT-PCR and nucleotide sequence analysis for EWS/FLI-1 chimeric mRNA. These results confirmed the diagnostic validity of the present tumor being a pPNET, thus raising the possibility that in the past, pPNETs which have arisen in the thorax of middle-aged and elderly patients have been mistakenly diagnosed as SCLC.

pPNET is a highly malignant tumor and patients with pPNET have a poor prognosis (15–17) with 2- and 6-year survival rates of 38% and 14%, respectively (16). After local recurrence, the mean survival rate is decreased to 11 months (17).

A standardized strategy against pPNET has not been established. Operation, combination chemotherapy or radiotherapy has been selected, but not satisfactory (15, 18). This tumor is thought to require an aggressive multimodality treatment consisting of preoperative and postoperative chemotherapy, radical surgical resection and postoperative irradiation, which may be performed preoperatively in selected cases (18).

References

8) Ambros IM, Ambros PF, Strehl S, et al. MIC2 is a specific marker for