Radiation Treatment for Malignant Small Cell Tumor of the Thoracopulmonary Region

Primitive Pluripotent Histogenesis and Differential Diagnosis

— A Case Report and Review of Literatures —

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Malignant small round cell tumor (SRCT) of the thoracopulmonary region appears to originate in the soft tissues of the chest wall or the peripheral lung. A differential diagnosis of poorly differentiated small round cell tumors which include Ewing's sarcoma of bone and soft tissue, embryonal rhabdomyosarcoma, Askin tumor, neuroblastoma, peripheral neuroectodermal tumor, small cell osteogenic sarcoma and lymphoma are often difficult by light microscopy alone. In recent, by the extensive studies electron microscopic examination, histochemical study, immunochemical study, cytogenetics and gene analysis, these tumors may be derived from the primitive and pluripotential cells, differentiating into mesenchymal, epithelial and neural features in variable proportions. Treatment for SRCT of thoracopulmonary region is not determined because of massive involvement of the lung, pleura or soft tissues of the chest wall resulted in a dismal outcome despite aggressive surgery, irradiation and chemotherapy.

Key Words: Malignant Small Cell Tumor of Thoracopulmonary Region, Radiation

CASE REPORT

A 44 year old male was admitted to a hospital with 3 months history of expanding mass on the left chest wall. On admission, he complanied of severe pain on left chest wall and the shoulder. Chest X-ray showed a well defined huge mass with hazy density in the left upper lung field and obliteration of aortic knob with slight downward displacement of left hilum (Fig. 1). There was cortical irregularity with moth-eaten appearance of axillary segment of left 2nd rib on rib series radiography. All of the laboratory data were within normal range. There was low density scattering calcified dot in the mass but fat plane between the mass and mediastinal structure was relatively well preserved on chest CAT scann (Fig. 2). The bone scann showed an increased uptake on anterior portion of left 2nd rib and left lateral chest wall and axilla area. Lung scan (99 mTc-MAA) showed perfusion defect on left upper lobe compatible with parenchymal lung disease.

Histopathologically (Fig. 3), the tumor was highly cellular and consisted of small, round monotonous cells. It showed proliferation of blood vessels with perivascular arrangement of tumor cells. The tumor cells showed round or ovoid nuclei, finely granular chromatin with inconspicuous small nucleoli. Their cytoplasm was scanty and mitosis is relatively frequent. Above findings are more consistent with to small round cell tumor originating in the thoracopulmonary region rather than small cell carcinoma of the lung. Because of there are neither evident rosette formation nor neurofibrillary background, it seems more close to extraskeletal Ewing's sarcoma. But PAS and other immunohistochemical studies including NSE and S-protein are not specific.

Radiation treatment was given by Cobalt (Theratron-780) teletherapy unit. Radiation field included a half of left lung and left shoulder in part. Radiation dose was 5,000 cGy delivered in 20 fractions in 5 weeks. It show remarkable tumor regression at 3,000 cGy in 2 weeks. At the completion of radiation treatment after additional 2,000 cGy irradiation at the residual tumor area, the tumor was regressed completely (Fig. 4). He tolerated irradiation well and achieved remarkable palliation of symptoms and signs.

DISCUSSION

We described a 44 years adult male with small round cell sarcoma, most probably extraskeletal Ewing's sarcoma in the thoracopulmonary region. Differential diagnosis of poorly differentiated small round cell tumors (SRCT) originating thoracopulmonary region[1] or chest wall[2~4], which include

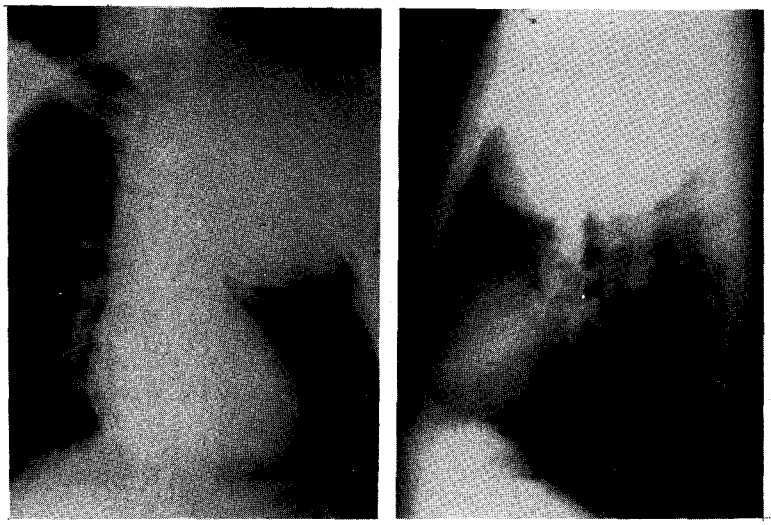

Fig. 1. *Chest PA and left lateral view shows huge well marginated soft tissue mass density in LUL with suspicious rib destruction and chest wall invasion. Mild shifting of trachea into right in direction is also noted.*

Ewing's sarcoma (ES) of bone and soft tissue, embryonal rhabdomyosarcoma, neuroblastoma, peripheral neuroectodermal tumors (PNET), small cell osteogenic sarcoma and lymphoma is often difficult by light microscopic examination alone. In recent[5], with the help of other laboratory methods such as electron microscopic study, histocytochemical and immunocytochemical stainings, cell culture and chromosomal analysis, many of the small round cell tumor may be categorized more accurately according to their histogenesis. But in spite of above extensive studies, its are impossible to decide distinct diagnosis because of many variants and the similarity in SRCT of the thoracopulmonary region.

Extraskeletal Ewing's sarcoma (E-ES) originating thoracopulmonary region or chest wall is a primitive small round cell neoplasm of soft tissues in children and young adults. By the report of Angervall L and Enzinger FM[6], out of 39 cases, the youngest patient was a 20-month-old boy, the oldest a 63-year-old woman. The median age was 20 and males slightly predominated over females. The median age was 20 and males slightly predominated over females. The principal sites of E-ES are chest wall, lower extremity and paravertebral region. The histologic features are very similar to the osseous Ewing's sarcoma (ES) with the exception that necrosis is not prevalent in the soft tissue lesion. Incomplete fibrovascular septa are responsible for the lobular appearance. Intracellular glycogen which stains a deep purple with the Periodic Acid-Schiff (PAS) preparation is more consistently in the soft tissue Ewing's sarcoma than in its skeletal counterpart. The ultrastructural findings are compatible in both neoplasms which the cells of both tumors possess rounded or ovoid nuclei with multiple minute nucleoli and small amounts of chromatin. The cytoplasm contains few organelles, including few mitochondria, a poorly developed Golgi apparatus and abundant glycogen. The lungs and the skeleton are the two common sites of metastasis. Prognosis is considered to be good when the treatment similar to that employed in Ewing's sarcoma of bone.

Embryonal rhabdomyosarcoma[7] affects mostly children younger than 10 years of age, but it also occurs in older patients occasionally. It closely resembles various stages in the embryogenesis of normal skeletal muscle, but its pattern is much more variable and ranges from poorly differentiated neoplasm, which are difficult to diagnose or defy diagnosis entirely. In many cases, a varying number of scattered cells with hyperchromatic nuclei and eosinophilic cytoplasm characteristic of rhabdomyoblast are noted.

Askin tumor (AT)[1,8,10] is a unique clinicopathologic entity characterized by a malignant small cell tumor of the thoracopulmonary region in children and young adults, first described by Askin, et

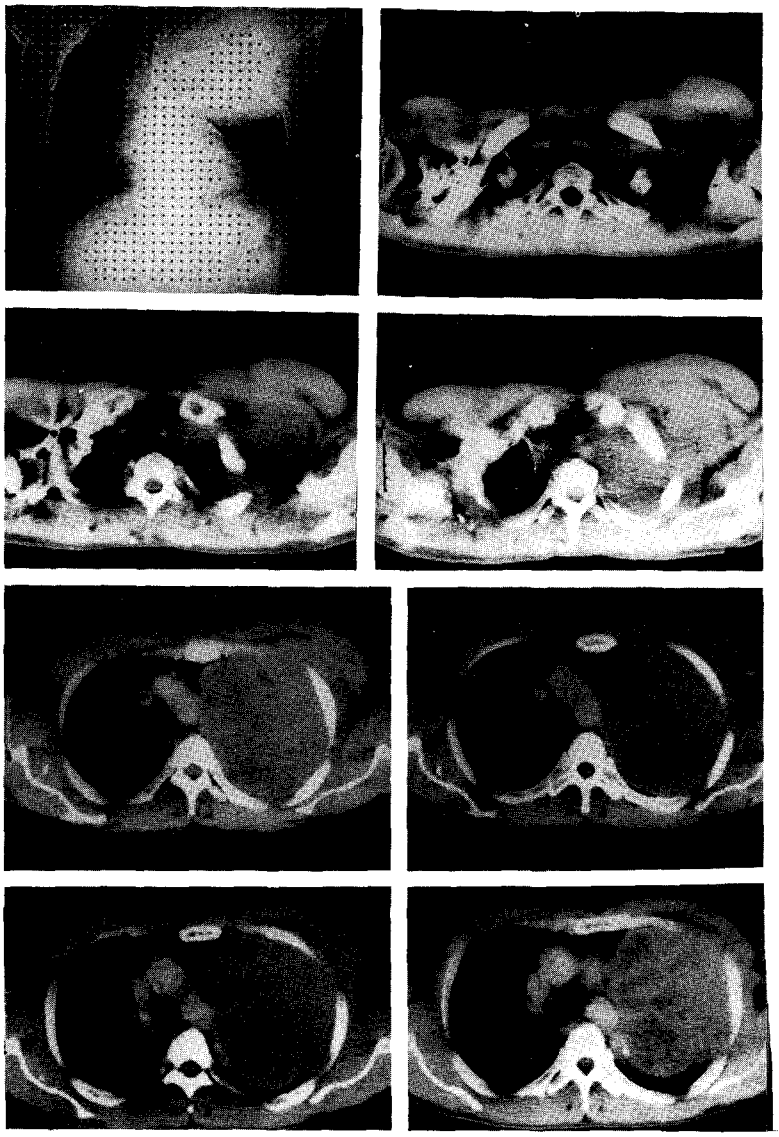

Fig. 2. Chest CT shows large inhomogenous mass in LUL with direct invasion into adjacent rib and chest wall. There are noted bulging of left upper chest wall and mild shifting of mediastinal into right side. It is no significant evidence of lymphadenopathy.

al., in 1979. By Lieberman[9], it was described as "PNET" bear a close resemblance to Extraskeletal Ewing's sarcoma. Their distinction is based on the presence of radially oriented peripheral cells, serpiginous bands of cells and pseudorosettes with a central acidophilic focus. Moreover, these tumors do not contain glycogen. The authors noted that ultrastructural features suggesting neural differentiation and dense core granule found in a few cases with AT. Linnoila, et al.[10], recently examined 15 similar tumors for the presence of neuron specific enolase (NSE), which they found in all cases. AT has been found to evidence certain neural features, such as expression of NSE, S-100 protein and neural ultrastructure (neurites, dense core granules). Because of Askin tumor tends to recur locally, prognosis is considered to be poor; the median survival was only 8 months.

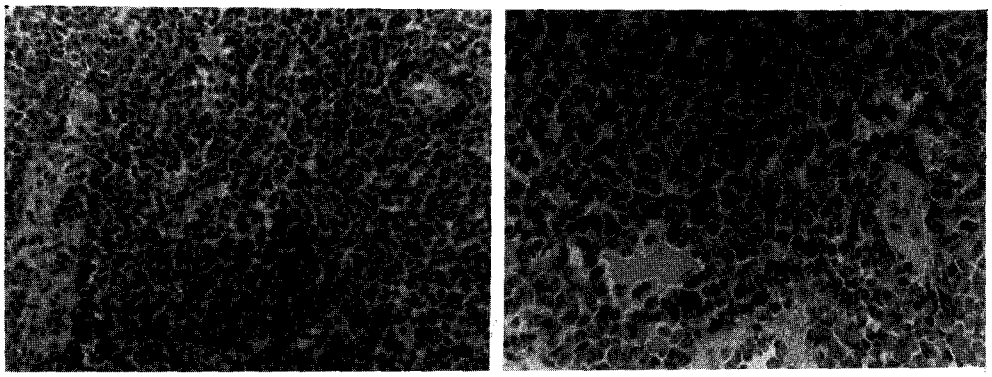

Fig. 3. Histopathologically, the tumor is highly cellular and consists of small rounded monotonous cells. The tumor does not show specific organoid structure. It shows proliferation of blood vessels with perivascular arrangement of tumor cells. The tumor cells show round or ovoid nuclei, finely granular chromatin with inconsipicous small nucleolei. There cytoplasm is scanty and mitosis is relatively frequent.

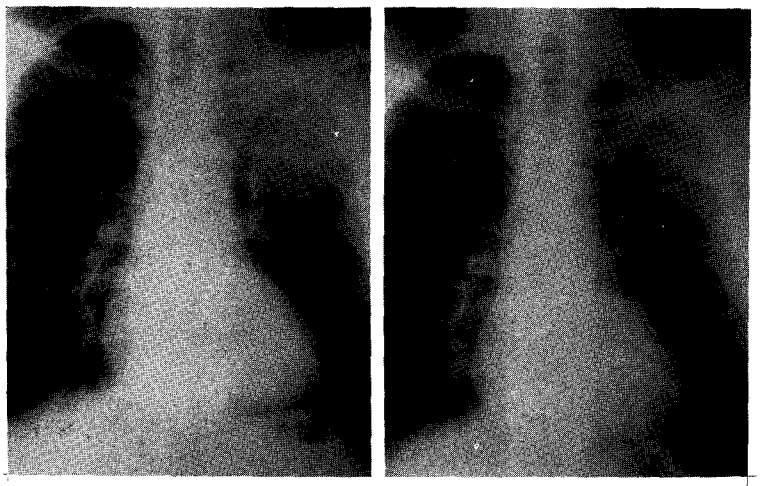

Fig. 4. After first 3,000 cGy irradiation, it shows remarkable decrease in size of LUL mass on chest PA and thereafter total 5,000 cGy irradiation it disappeared huge tumor mass nearly.

Immunocytochemical studies[2,5,9,11,13] demonstrated that CEA (Carcinoembryonic antigen), NSE (Neuron specific enolase), vimentin, cytokeratin, EMA, desmin and S-100 protein, many of the SRCT may be categorized more accurately. CEA is often present in gastrointestinal tumor, although CEA is not a useful marker in the differential diagnosis of these tumors because of a lack of its specificity. NSE has been believed to be highly specific for neurons and neuroendocrine cells. NSE is positive in neuroblastoma and primitive neuroectodermal tumors, but many authors reported that NSE is negative in Ewing's sarcoma. Therefore Tsokos, et al.[9,11], reported the usefulness of NSE in identifying of neural tumors and other SRCT. But NSE has been recently found in normal and neoplastic tissues other than those of the nervous and neuroendocrine systems, so the specificity of NSE may be equivocal. Vimentin, which consistently presents in ES, is found in all forms of mesenchymal and some epithelial tissues, but the former is reported as negative in ES.

Peripheral primitive neuroectodermal tumors (PNET) are also classified into a type of SRCT and

often difficult to distinguish from E-ES and Askin tumor. However, PNET[10,12,13] are characterized by the features of neuroectodermal histogenesis and differentiation, such as Homer-Wright rosettes, neurites, neurofilaments, neurosecretory granules. Regarding immunocytochemical findings, NSE is positive in most of cases with PNET, but S-100 protein, NF, vimentin and cytokeratin are positive in some. Despite the extensive search, our case showed no distinct feature as in neuroectodermal differentiation because of NSE and S-100 protein negativity. We are also unable to diagnose our case as PNET. More recently Moll, et al.,[14] reported that in ES, vimentin, desmoplakin and cytokeratin are positive and NF is sometimes also positive. These findings suggested that ES might be derived from a primitive pluripotential cell that may differentiate, in variable proportions, into cells with mesenchymal, epithelial and even neural features. The concept of ES and its relation to PNET and Askin tumor are in flux, the distinction of these tumors is virtually very difficult not only at the light and electron microscopic studies but also in immunocytochemical studies. Cytogenetic analysis[15,16] disclosed rep (11;22) translocation, a consistent reciprocal translocation t (11;22), (q24;q12) has been reported in direct preparation of tumor cells and cell lines derived from ES-B (Ewing's sarcoma, bone).

The same abnormality was also subsequently detected in E-ES, PNET and Askin tumor. These tumors seem to have a same oncogenesis. Askin tumor, PNET and ES possess an indistinguishable cytogenetic abnormality and express a similar pattern of oncogenes. These findings suggest a possible common histogenesis of these tumors. It speculate that ES may be primitive pluripotential cell that differentiate into cells with mesenchymal, epithelial and neural features, in variable proportions. And some tumors diagnosed as PNET or Askin tumor might be belong to ES that differentiates to neural feature in various degrees. These comprehensive studies might to shed some light to a certain aspect regarding histogenesis and oncogenesis in these tumors.

Treatment result[1,17] for SRCT of the thoracopulmonary region is poor despite aggressive surgery, irradiation and chemotherapy. For radiotherapy, dose was not stated in most case reports. But in reported cases, it varied from 3,500 to 5,500 cGy. The chemotherapy was given generally as combinations of drugs that most frequently included cyclophosphamide, actinomycin D and vincristine. Methotrexate, 5-FU, adriamycin d-dacarbazine (DTIC) were the other drugs. By the report of Askin, et al., the survival data have been noted. Fourteen of the 18 evaluable patients died at intervals varying from 4 to 44 months (median 8 months) after diagnosis. Recurrence and metastasis is the most common of chest wall, pleura, diaphragm and ipsilateral lung.

In conclusion, to determine whether these diagnoses shall be determine a group of small cell tumors originating in the thoracopulmonary region with unique biologic behavior and identifiable pathologic characteristics, clinical and treatment response data were compiled, and electron microscopic and immunohistochemical studies were done for those patients with adequate samples.

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= 국문초록 =

흉폐부에서 발생한 악성소세포 종양의 방사선치료

국립의료원 치료방사선과

오 원 용 · 양 진 영 · 황 인 순

흉폐부 또는 흉벽에서 발생하는 악성소세포 종양군인 Ewings sarcoma, 횡문근육종, Askin tumor, 신경아세포종, PNET, 임파종 등은 현미경학적 소견만으로는 감별하기 어렵다. 그러나 최근에는 조직세포화학적검사, 면역세포화학적검사, 세포배양, 세포유전학적 검사등의 도움으로 상기한 악성소세포 종양군들이 모두가 같은 계통의 primitive pluripotent cells로 부터 분화되어 발병되는 것으로 확인되였다. 치료는 외과적 절제술, 방사선치료, 항암요법 등이 시도되고 있으나 예후는 재발과 원격전이로 인하여 불량한 것으로 보고되고 있다. 본 저자들은 본원에서 치료한 예를 보고하면서 흉폐부에서 발생하는 악성소세포 종양군의 조직발생과 감별진단에 대하여 논하고자 한다.