of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

Acknowledgment

We would like to thank Mika Nagai for her assistance in the preparation of this manuscript.

Conflict of interest statement

None declared.

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Pathology International 2007; **57**: 627–631 doi:10.1111/j.1440-1827.2007.02150.x

Case Report

Diffuse-type giant cell tumor/pigmented villonodular synovitis arising in the sacrum: Malignant form

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Diffuse-type giant cell tumor (GCT)/pigmented villonodular synovitis (PVNS) in the axial skeleton or spine is rare. Herein is reported a case of diffuse-type GCT/PVNS involving the sacrum and the fifth lumbar vertebra, in which the patient developed regional lymph node swelling after recurrence. The recurrent tumor was found to have atypical histological features such as spindle cell morphology, cytological atypia and high mitotic rate, which are compatible with the diagnostic criteria of secondary malignant diffuse-type GCT/PVNS. Although the nodal lesions were not sampled histologically, the clinical and histological features indicate that the current case is an example of malignant diffuse-type GCT/PVNS. This case is considered to be the first case of malignant diffuse-type GCT/PVNS in the spine, because no such lesions have been previously reported in the axial skeleton or spine. Careful surveillance should be required for diffuse-type GCT/PVNS arising at unusual site.

Key words: malignant diffuse-type giant cell tumor, metastasis, pigmented villonodular synovitis, sacrum, spine

Diffuse-type giant cell tumor (GCT), which is a synonym of pigmented villonodular synovitis (PVNS), usually arises from the joint spaces in large joints, such as knee and hip.[1] Histologically, the lesion is villous and infiltrative. Characteristically, it has a pseudoglandular or pseudoalveolar pattern.[1,2] The tumor is mainly composed of small or large histiocytic cells and giant cells. Local recurrence is common, and it often disturbs the function of the joint.

Diffuse-type GCT/PVNS rarely affects the spinal vertebra, wherein it arises from the articular facet joint.[3] Half of the lesions have been reported to occur in the cervical spine. Radiographically, it is a destructive and osteolytic lesion involving the posterior facet joint, accompanied by a soft-tissue component. The recurrence rate has been reported to be 18%.[3] Its lumbo-sacral involvement is relatively rare. Herein we report a case of PVNS that mainly involved the sacrum with a large osteolytic lesion, where the patient developed regional lymph node swelling after recurrence. The histological features of the recurrent tumor were convincing evidence of secondary malignant form of diffuse-type GCT/PVNS. To the best of our knowledge there have been no previous reports of malignant diffuse-type GCT/PVNS involving the spine and axial skeleton.

CLINICAL SUMMARY

A 53-year-old woman complained of a 5 month history of numbness and pain from the left buttock to the lower leg. Muscle weakness of the lower extremities was not apparent. Laboratory data showed no remarkable changes. Plain radiography showed an irregular osteolytic lesion with cortical destruction in the left side of the sacrum. CT revealed an osteolytic lesion in the lateral vertebra and facet of S1, associated with a posterior soft-tissue mass, which measured 5 × 4 cm (Fig. 1a). Magnetic resonance imaging (MRI) demonstrated a mass on T1-weighted imaging (WI) of low intensity (Fig. 1b) and on T2-WI of intermediate intensity. The mass involved the S1 and L5 vertebral body, and was extending toward the posterior elements of the vertebra and posterior soft tissue. The tumor also involved the facet joint between S1 and L5. Bone scintigraphy showed no abnormal uptake, except for the lumbo-sacral area. After open biopsy,

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This case report was presented in part at the 33rd Annual Closed Members' Meeting of the International Skeletal Society held in Vancouver, Canada, September 2006.

Received 10 April 2007. Accepted for publication 17 May 2007.

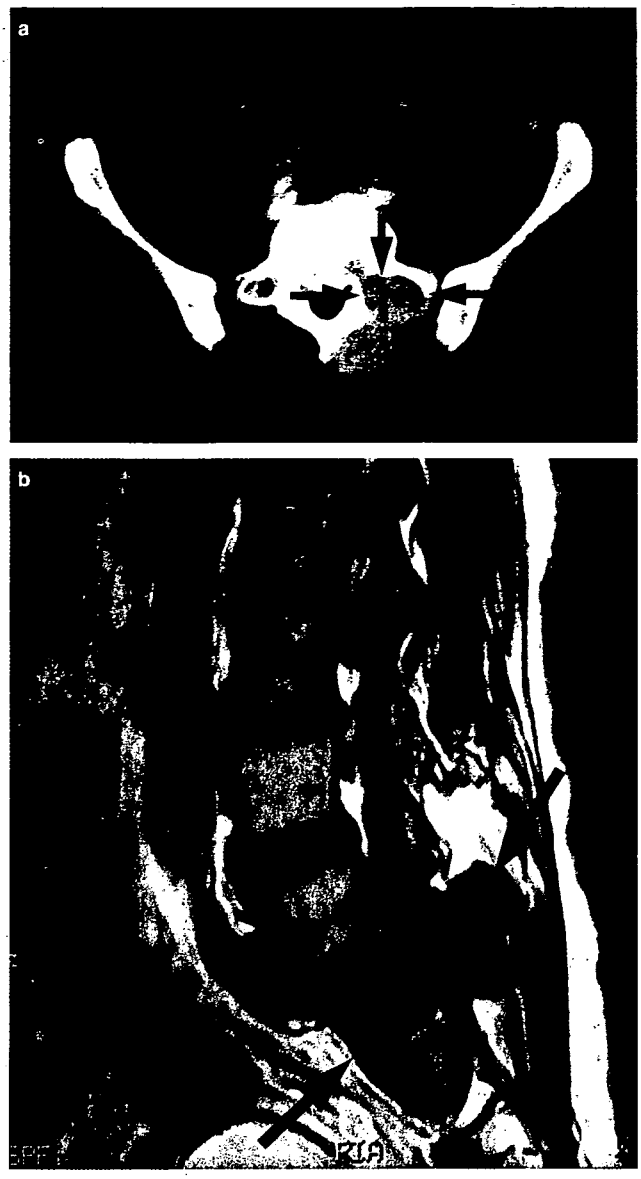

Figure 1 (**a**) CT of an osteolytic lesion in the lamina and facet joint with a posterior soft-tissue mass (arrows). (**b**) Magnetic resonance T1-weighted image of a mass lesion in the vertebral body and posterior elements of S1 and L5 (arrows).

tumor resection and curettage followed by auto-bone graft were performed. Ten months after the surgery, local recurrence was detected on MRI and en bloc resection was performed for the recurrent tumor. Follow-up MRI demonstrated a second recurrence and swelling in the left inguinal (Fig. 2a) and para-aortic (Fig. 2b) lymph nodes, 7 months after the second surgery. However, these nodal lesions were not sampled histologically. The patient underwent chemotherapy (high-dose ifosphamide, cyclophosphamide, adriamycin, vincristine) for both the recurrence and the possibility of the nodal metastatic lesions.

PATHOLOGICAL FINDINGS

Grossly, the fragmentally resected initial surgical specimen was a brownish color with focal whitish or yellowish areas. Microscopically, biopsy and resected specimens indicated essentially the same findings. Although a typical villous pattern was not evident, a pseudoglandular pattern was seen on low-power view (Fig. 3a). The tumor was mainly composed of histiocytic cells with eosinophilic cytoplasm, accompanied by hemosiderin deposits in their cytoplasm (Fig. 3b). Osteoclast-like multinucleated giant cells were scattered throughout the lesion (Fig. 3c). Aggregates of xanthoma cells (Fig. 3d) and chronic inflammatory infiltrate were also prominent throughout the tumor. Mitotic figures were occasionally seen (0–1/10 high-power fields (HPF)), but abnormal ones were never detected. The recurrent tumor had a nodular and infiltrative growth pattern (Fig. 4a). The tumor was mainly composed of a cellular proliferation of rounded or oval cells with deeply eosinophilic cytoplasm and mild nuclear pleomorphism (Fig. 4b), accompanied by scattered osteoclast-like multinucleated giant cells. Focally, short spindle-shaped cells were arranged in fascicles (Fig. 4c). Mitotic figures were frequently seen (38/10 HPF). No tumor necrosis was detected in any part of the tumor. Immunohistochemically, mononuclear cells and osteoclast-like multinucleated giant cells of the primary tumor were positive for CD68 (KP-1; 1:300; Dako Cytomation, Glostrup, Denmark). Mononuclear histiocytic cells had no immunoreactivity for desmin (D33; 1:100; Dako Cytomation) or S-100 protein (polyclonal; 1:400; Dako Cytomation). A total of 5.6% of the mononuclear cells of the primary tumor were positive for Ki-67 (MIB-1; 1:100; Dako Cytomation). Only small numbers of mononuclear cells in the recurrent tumor were positive for CD68, while multinucleated giant cells were constantly positive for CD68. A total of 21.25% of the mononuclear cells were positive for Ki-67 in the recurrent tumor (Fig. 4d). No tumor cells in the primary or recurrent tumor were immunoreactive for p53 (PAb 1801; 1:100; Oncogene Research Products, San Diego, CA).

DISCUSSION

The occurrence of diffuse-type GCT/PVNS in the spine is rare. The vast majority of the cases affect the cervical and lumbar regions (41%).[3] The current case occurred mainly in the sacrum, but also involved the fifth lumbar vertebra. According to Giannini *et al.* only three cases involved the L5–S1 region.[3–5] Previously reported cases of spinal diffuse-type GCT/PVNS frequently involved the facet joint, therefore spinal diffuse-type GCT/PVNS is considered to originate from the synovial membranes that line the diarthrodial joints of the vertebral arches. The left facet joint between L5 and S1 was also affected in the present case. The symptoms and signs of

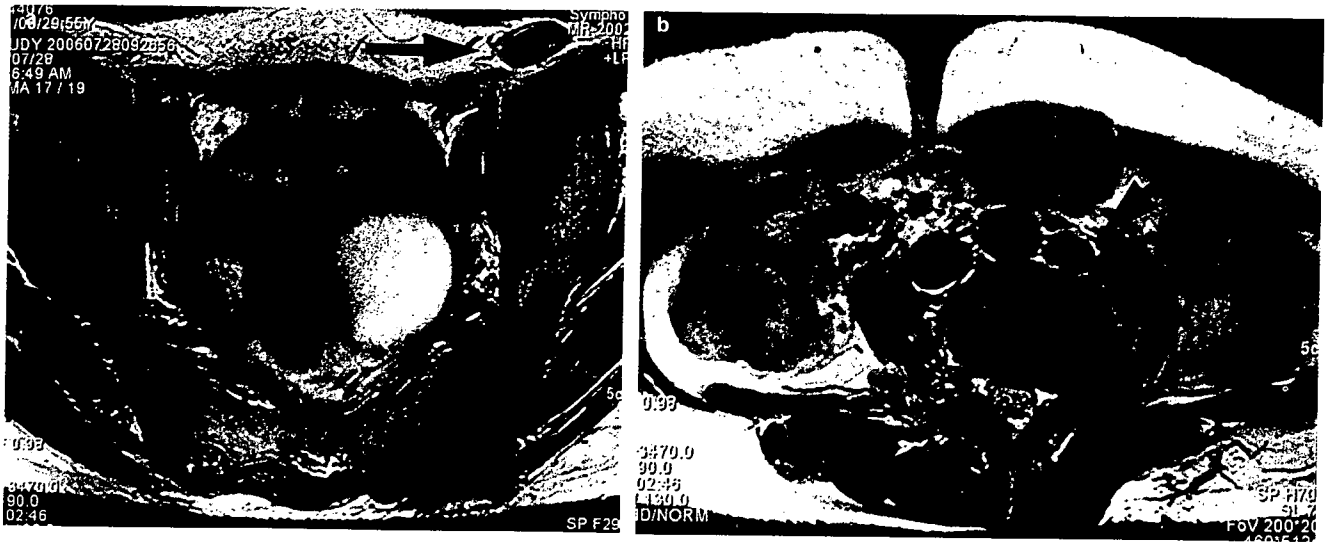

Figure 2 Magnetic resonance imaging of multi-nodular swelling of the (**a**) left inguinal (arrow) and (**b**) para-aortic (arrow) lymph nodes, indicating lymph node metastases.

spinal diffuse-type GCT/PVNS were similar to those of other spinal epidural tumoral masses, according to their location. The present case mainly presented sciatica. Concerning the clinical outcome, Giannini *et al.* reported that although the local recurrence rate was relatively high, repeated surgical excision appeared to be curative.[3]

Anatomically, the present case had an osteolytic lesion without mineralization mainly in the sacrum. Therefore, considering the histological features, the differential diagnosis of the current primary lesion are giant cell-containing osteolytic lesions, including GCT, aneurysmal bone cyst (ABC), chondroblastoma, chondromyxoid fibroma, giant cell reparative granuloma, brown tumor and osteoclast-rich osteosarcoma. The sacrum is the most common primary site in the axial skeleton of GCT. GCT frequently contains aggregates of foamy cells as seen in diffuse-type GCT/PVNS. However, GCT usually involves the vertebral body and its multicentric occurrence is very rare.

Malignant diffuse-type GCT/PVNS or malignant giant cell tumor of tendon sheath (GCTTS) is an extremely rare condition[6–11] and its definition is given as a benign GCTTS or diffuse-type GCT/PVNS, which coexists with frankly malignant areas, or given as the original lesion is typically benign GCTTS or diffuse-type GCT/PVNS with a recurrent lesion that appears to be malignant.[2,9] According to Bertoni *et al.* 75% of cases occur in the knee joint.[9] Half the patients with malignant diffuse-type GCT/PVNS develop distant metastasis and die of the disease, thus making it a very aggressive malignant tumor. Based on pathological features and clinical presentation, there is a possibility that the present case is an example of the latter condition because of the regional lymph node swelling and malignant histology in the recurrent lesion.

Most cases of malignant diffuse-type GCT/PVNS have been reported to occur in large joints in the extremities such as the knee, ankle or foot.[9] The present case affected mainly the sacrum and the fifth lumbar vertebrae. There have been no case reports of malignant diffuse-type GCT/PVNS arising in the axial skeleton or spine.

Bertoni *et al.* documented eight cases of malignant diffuse-type GCT/PVNS and stated that the important histological features of malignancy were (i) a nodular or solid infiltrative pattern; (ii) large, plump, round or oval cells with deep eosinophilic cytoplasm and indistinct borders; (iii) large nuclei with prominent nucleoli; and (iv) necrotic areas.[9] Although the present recurrent tumor had no necrotic areas, a nodular and infiltrative growth pattern, and cellular proliferation of rounded or oval cells were both evident. In addition, mitotic figures were frequently seen (maximum: 38/10 HPF) and cellular fascicles of spindle-shaped cells were noted in part. Somerhausen and Fletcher reviewed 50 cases of extra-articular diffuse-type GCT/PVNS and found seven cases of malignant/atypical histological features and/or malignant behavior.[10] Among them, two patients developed distant metastases. One patient had spindle cell morphology with high mitotic activity (up to 25/10 HPF) at the primary site, whereas the other patient had the usual benign morphology, even at the metastatic site. Somerhausen and Fletcher stated that atypical features such as increased mitotic activity, necrosis, spindle morphology and cytological atypia are not indicative of malignancy when present individually. The highest mitotic count was 26/10 HPF in their series. In the present case, there was an invasion into the medullary cavity of the sacrum in the primary tumor. Moreover, the present case also had combined histological atypical features com-

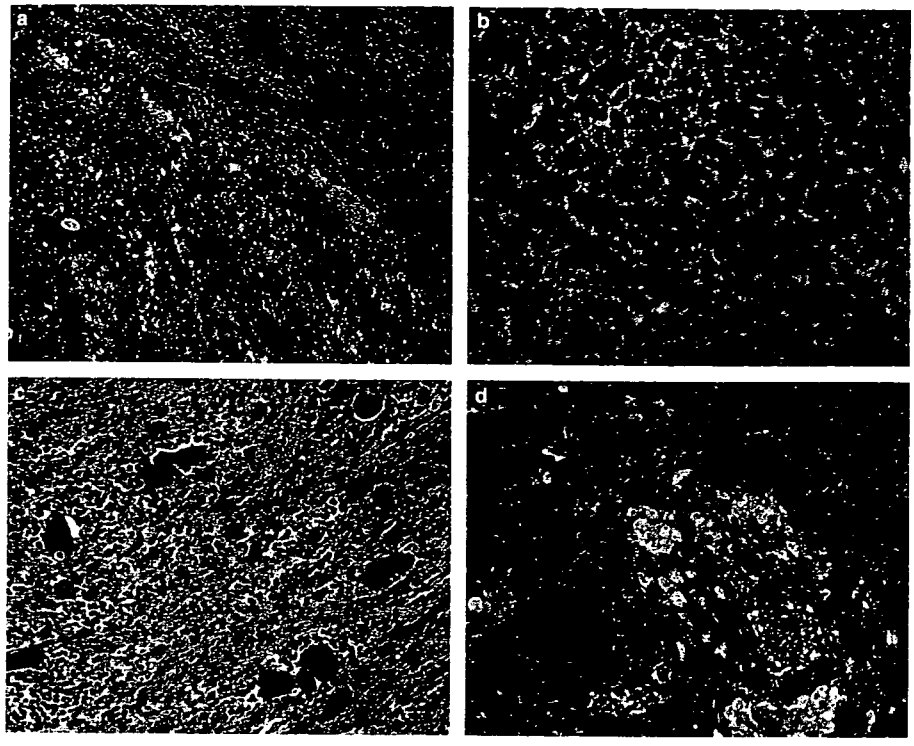

Figure 3 (**a**) Pseudoglandular pattern of the primary benign diffuse-type giant cell tumor/pigmented villonodular synovitis on low-power view. (**b**) Rounded or polygonal mononuclear cells with eosinophilic cytoplasm and intracytoplasmic hemosiderin. (**c**) Scattered osteoclast-like multinucleated giant cells. (**d**) Aggregates of xanthoma cells intermixed with rounded cells.

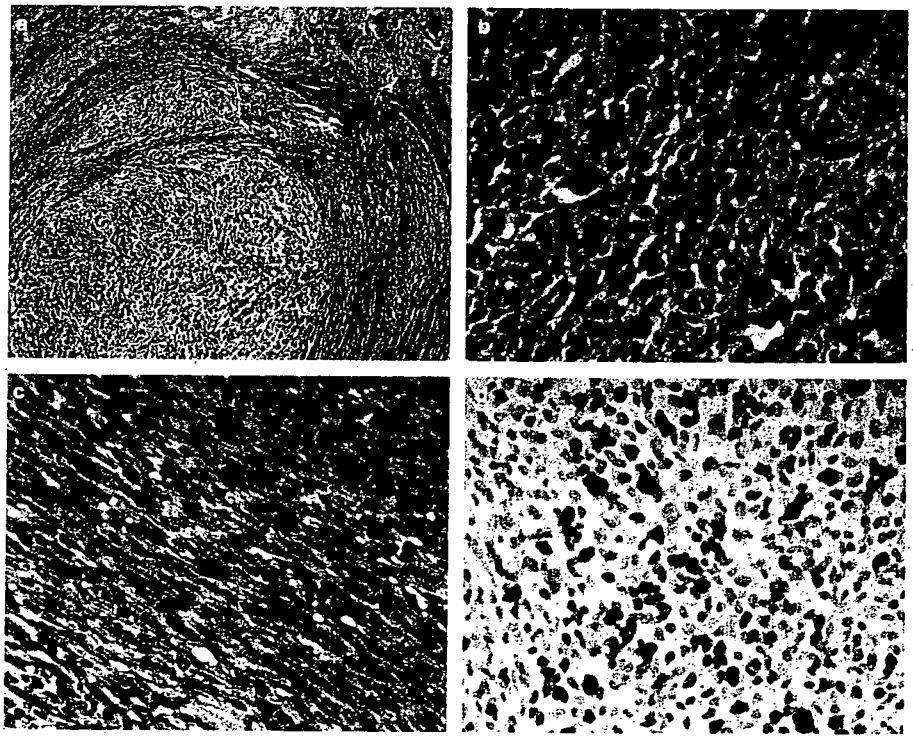

Figure 4 (**a**) Nodular or infiltrative growth pattern of the recurrent tumor in the fibro-collagenous tissue. (**b**) Rounded mononuclear cells with deeply eosinophilic cytoplasm showing mild nuclear pleomorphism. (**c**) Cellular proliferation of ovoid or short spindle-shaped cells in a fascicular arrangement. Note the frequent mitotic figures in these cells. (**d**) High proliferating activities as shown by frequent Ki-67-positive cells (21%).

prising spindle cell morphology, cytological atypia and a very high mitotic rate in the recurrent tumor. Therefore, the clinical and histological features of the current case confirm that this is an example of malignant diffuse-type GCT/PNVS.

In conclusion, we describe a case of PVNS arising in the sacrum, with malignant histology after local recurrence. It was difficult to predict its aggressive biological behavior when reviewing the histological findings of the primary

tumor, therefore careful surveillance is required for histologically typical diffuse-type GCT/PVNS arising at an unusual site.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (18590332), Tokyo, Japan. The English used in this manuscript was revised by Miss K. Miller (Royal English Language Center, Fukuoka, Japan).

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日小血会誌 21: 172-175, 2007

症例報告

ホジキンリンパ腫の治療後に発症した二次がんの2例

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Two Cases of Hodgkin's Lymphoma Developed Second Malignancy after Completion of the Treatment

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Abstract Case 1 is a 34-year-old woman who developed Hodgkin's lymphoma (HL) of stage III at 16 years of age and received chemoradiotherapy. The disease relapsed at 19 years of age and underwent second-line chemotherapy in combination with splenectomy and radiotherapy. At 33 years of age, 13 years after completion of the treatment of HL, she developed an undifferentiated sarcoma. Therefore, she received chemotherapy and surgery and remained in complete remission (CR) for more than 52 months. Case 2 is a 20-year-old man who developed HL of stage III at 4 years of age and received chemotherapy without radiotherapy, concerning the risk of late adverse effect. At 20 years of age, 14 years after completion of the treatment of HL, he developed a non-Hodgkin's lymphoma (NHL) of gastric mucosa for which chemo- and radiotherapy were administered, resulting in CR for 13 months. In Western countries, the reported incidence of second malignancy after the treatment of HL is so high that 20% of HL patients died of second malignancy. On the other hand, only a few patients with second malignancy after HL were reported in Japan. Because of low incidence of HL compared to Western countries, the long-term follow-up system is not yet established in Japan. Therefore, the number of second malignancy among survivors of HL would increase in the future when a nationwide follow-up system is organized.

要 旨 症例1は34歳の女性．16歳時にホジキンリンパ腫（HL）を発症し，化学療法と放射線治療を受けた．19歳時に再発し化学療法，放射線治療と脾臓摘出術を受けた．13年後の33歳時にundifferentiated sarcomaを発症し，化学療法と手術を受け，52カ月間寛解を維持している．症例2は20歳の男性．4歳時にHLを発症し，化学療法を受けた．14年後の20歳時に非ホジキンリンパ腫（NHL）を発症し，化学療法と放射線治療を受け，13カ月間寛解を維持している．欧米ではHL後の二次がんの発症率は高いが，本邦ではまれである．しかし本邦における全国規模でのフォローアップ体制が確立されていないことや，本邦からの多数例の報告においても観察期間が短いことを考慮すると，HL治療後の二次がん発症の実態を明らかにするために，長期にわたる経過観察の必要性が示唆された．

Key words: Hodgkin's lymphoma, second malignancy, undifferentiated sarcoma, post radiation sarcoma, second non-Hodgkin's lymphoma

2007年3月26日受付，2007年5月17日受理
別刷請求先：〒811-1356 福岡市南区野多目3-1-1
九州がんセンター小児科 稲垣二郎
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I. はじめに

小児ホジキンリンパ腫（Hodgkin's lymphoma: HL）はわが国では非常にまれな疾患であり，その発症頻度は全小児がんの4%を占める欧米と比較すると，約1/10程度と推測されている[1-3]．欧米においては，従来標準的治療

とされてきた放射線照射と化学療法の併用で高い長期生存率が得られるようになったが，晩期合併症，とりわけ二次がんを高率に発症することが知られている[4-9]．一方，わが国の HL 157 例の後方視的検討によれば，二次性腫瘍の発症は 1 例のみであった[10]．今回われわれは，HL の治療終了 13 年後と 14 年後に，それぞれ右背部の undifferentiated sarcoma と非ホジキンリンパ腫（non-Hodgkin's lymphoma: NHL）を発症した 2 症例を経験したので報告する．

II. 症　　例

1. 症　例　1

患者：34 歳，女性．

主訴：右背部腫瘤．

既往歴：16 歳 1 カ月時に HL（結節硬化型，stage III（頸部，腹部））を発症し，COPP 療法（サイクロフォスファマイド，ビンクリスチン，プレドニゾロン，プロカルバジン）6 コースと放射線照射 30Gy（全腹部照射＋マントル型照射）を受けた．19 歳 11 カ月時に HL の再発（肝，大動脈周囲リンパ節，脾）が認められ，脾臓摘出術と ABVD 療法（ドキソルビシン，ブレオマイシン，ビンブラスチン，ダカルバジン）を 7 コース，局所照射 35Gy を施行された．今回の背部腫瘤はこの照射野に含まれていた．

家族歴：特記事項なし．

現病歴：33 歳 2 カ月時に右背部の腫瘤に気づき，MRI で L2 から L4 レベルの右傍脊柱筋内に T2WI で high intensity を呈する腫瘍が認められた．切開生検で診断に至らず，広範切除術を施行され malignant giant cell tumor と診断された．その後外来で経過観察されていたが，34 歳 11 カ月時に MRI で局所再発が認められ，生検の結果，骨肉腫類似の組織像を呈する post radiation sarcoma と診断された．

治療経過：イフォスファミドとビンクリスチン，ドキソルビシンとサイクロフォスファマイドからなる化学療法を 2 コースずつ施行したが，種々の合併症により化学療法の継続が困難となったため，腫瘍広範切除術を施行し治療終了とした．その後 52 カ月間再発を認めていない．

2. 症　例　2

患者：20 歳，男性．

主訴：嘔吐，体重減少．

既往歴：4 歳 10 カ月時に HL（混合細胞型，stage III（頸部，腹部））を発症し，COPP 療法を 12 コース施行された．晩期障害を考慮して放射線治療は行わなかった．

幼少時より肺炎を繰り返しており，7 歳時に IgG 4 サブクラス欠損症と診断された．

家族歴：特記事項なし．

現病歴：19 歳 6 カ月時に心窩部痛，嘔吐，体重減少が出現した．胃内視鏡検査と病理組織検査で胃炎（*Helicobacter pylori* 陽性）と診断され，プロトンポンプインヒビターの投与で症状は軽快した．20 歳 7 カ月時，経過観察のための内視鏡検査で胃角部に潰瘍を認め，病理組織検査で NHL と診断された．

入院時現症：体重 45.0 kg，身長 156.1 cm．心音，呼吸音ともに異常なし．腹部は軟，肝脾腫を認めず，表在リンパ節を触知しなかった．

入院時検査所見：末梢血液検査，生化学検査では異常を認めなかったが，sIL-2R は著明に上昇（1993U/l）していた．骨髄所見は正常であった．

画像所見：診断時の胃内視鏡写真（Fig. 1）では胃角部から前庭部大彎後壁に潰瘍性病変を認めた．胃十二指腸造影検査では胃角から前庭部に不整な陥凹性病変を認めるが筋層浸潤はなく，CT と Ga シンチで他病変を認めなかった．

病理組織所見（Fig. 2）：大型で好塩基性の強い細胞質をもった異型リンパ球をびまん性に認め，免疫染色は CD20，CD30，CD79a，LCA が陽性であり，diffuse large B-cell lymphoma と診断された．ホジキン細胞や Reed Sternberg 細胞は認めなかった．

治療経過：胃原発の diffuse large B-cell lymphoma stage I として，CHOP 療法（サイクロフォスファマイド，ビンクリスチン，プレドニゾロン，ドキソルビシン）を 3 コース施行し，組織学的に寛解を確認した．その後，放射線を全胃に 30Gy 照射した．原発巣には 10.5Gy 追加照射し，治療を終了した．その後 13 カ月間寛解を維持している．

III. 考　　察

小児 HL の治療は，放射線療法から始まったが，1970 年代に多剤併用化学療法の有効性が示され，欧米において放射線療法と化学療法とを併用することで，長期生存率は 90%を超えるようになった．一方で，二次がん，性腺障害，成長障害や心・肺合併症などの重篤な晩期障害が報告されるようになり[11,12]，その中でも二次がんの累積発症率（15〜30 年）は 7〜26.3%と高率であり[4-8]，相対危険度は 7〜18.5 であった[9,13]．二次がんはおもに固形癌，急性白血病，NHL であり，これらの報告の中では放射線治療歴，照射線量，照射と化学療法の併用，アルキル化剤投与歴，化学療法の積算量，診断時年齢，摘

Fig. 1　Endoscopic examination of case 2 showed the ulcerative lesions (arrow) on the posterior wall in the corpus of the stomach

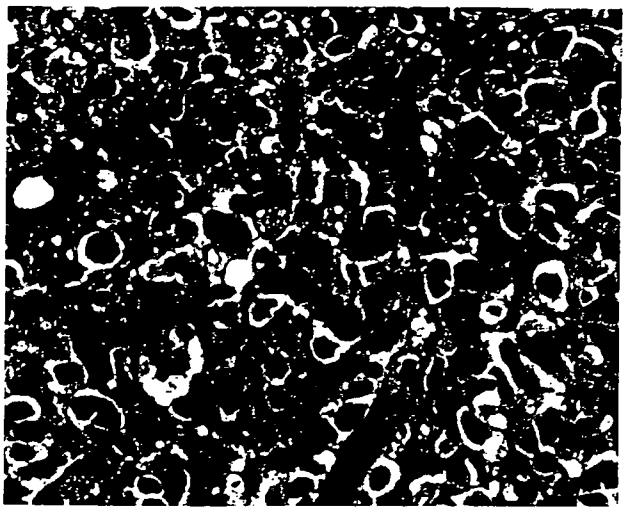

Fig. 2　Histopathological image of the biopsied specimen of the gastric mucosa of case 2
The section showed patchy and diffuse infiltration of large atypical lymphocytes with pale cytoplasms. No typical Hodgkin's cells or R-S cells were detected.

脾などがリスク因子として報告されている[4-9]．このため近年では，化学療法のコース数を減じたり，アルキル化剤を省略したりするようになってきており[14,15]，さらに，限局期だけでなく進行期においても，化学療法後に完全寛解となった場合に放射線療法を省略できるかどうかについて，多くのランダマイズ試験で検討されている[16-18]．一方，本邦ではHLの発症率が非常に低いために標準的治療が確立されておらず，施設により異なる治療がなされてきた．日本小児白血病/リンパ腫研究グループによるHL 157例の後方視的検討によれば[10]，わが国の治療はCOPP＋ABVDのレジメンが一般的で非照射例が半数を占めていたが，全体の成績は欧米と同等であり二次性腫瘍の報告はデスモイド腫瘍の1例のみで発症率は0.6%であった．しかし，HLに対するフォローアップ体制が確立されていないことや，観察期間が約5年と短いことを考慮すると，二次がんの発症が少ないことが，非照射例が多いことに起因しているかどうかは現時点では不明であると思われる．Bhatiaらの小児HL 1,380例の報告によると，アルキル化剤を含む化学療法が二次性の白血病とNHLのリスク因子で，発症の中央値はHLの治療終了から14年であった[4]．自験例の症例1は照射野からの発症であるが，症例2では幼児期にHLを発症したため，晩期障害のリスクを考慮して放射線治療を行わなかったので，二次性NHLのリスク因子となったのはアルキル化剤（サイクロフォスファマイド，プロカルバジン）と考えられる．上述した本邦の調査では，非照射レジメンで治療された症例の割合は多かったが，化学療法のコース数は多い傾向があり，また観察期間も短いため，今後二次がんを発症する症例の増加が予想される．今回報告した2症例の治療の比較を示した（Table 1）．当施設では過去に17例のHLを治療しており，そのうち2症例に二次がんが発症したことは，本邦におけるHL治

Table 1　Treatment summaries in two patients with HL

	Case 1	Case 2
Cumulative dose of chemotherapy (mg/m²)		
COPP		
Cyclophosphamide	3,724	5,375
Vincristine	17	30
Procarbazine	11,200	16,800
Prednisolone	3,360	6,720
ABVD		
Doxorubicin	350	0
Bleomycin	140	0
Vinblastine	84	0
Dacarbazine	5,250	0
Cumulative dose of radiotherapy (Gy)		
Whole abdomen	30	0
Mantle field	30	0
Local	35	0
Surgery	Splenectomy	(−)

療後の二次がんの発症率の高さを示唆しているものと思われる．また2症例ともHLの治療終了後10年以上経過してからの発症であり，長期にわたる経過観察の必要性がうかがえる．さらに欧米からの報告では，HL治療後の二次がんはHLの死亡原因の20%を占めており，その予後は不良である．二次性NHLの発症率は0.4～3%で[4-8]，化学療法単独，放射線療法単独，両者の併用および造血幹細胞移植のいずれにも反応性が乏しく，Rueffer らによれば2年生存率は30%と報告されており[6]，Ng らの報告でも5年生存率は50%程度に過ぎない[8]．自験例の2症例は現在のところ，それぞれ52カ月間と13カ月間寛解を維持しているが，今後も注意深い経過観察が必要である．

HLに対する治療の今後の課題は，現在の高い生存率を維持しつつ，いかに晩期障害のリスクを減らせるかであり，放射線照射線量とアルキル化剤をどこまで減量，あるいは省略できるかという点においての検討が必要である．そのためには，過去に報告されている症例の追跡調査体制を確立すると同時に，統一された治療プロトコールによる多施設共同研究が組織されることが必要と思われた．

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Japanese Journal of Clinical Oncology Advance Access published November 12, 2007

Jpn J Clin Oncol
doi:10.1093/jjco/hym108

Case Report

Primary Ewing's Sarcoma Family Tumors of the Lung – a Case Report and Review of the Literature

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Received March 25, 2007; accepted July 8, 2007

Ewing's sarcoma family tumors (ESFT) have been reported to originate in a variety of sites, most commonly in the extremities. We herein report a case of a primary ESFT of the lung presenting in an 8-year-old boy. A histological examination of hematoxylin–eosin stained sections showed a homogeneous population of closely packed small neoplastic cells. The tumor cells were strongly positive for CD99/MIC2 and negative for the leukocyte common antigen, myoglobin, desmin, epithelial membrane antigen, AE1/AE3 and synaptophysin. The patient was treated with neoadjuvant chemotherapy and surgery. Nine months later, he is in good condition and chest CT scans have revealed no evidence of either local recurrence or distant metastasis. Cases of ESFT of the lung have been reported in recent years but there are still few reports of primary ESFT of the lung. To date, only eight cases of ESFT of the lung have been reported in the literature. This is the first report of an ESFT of the lung occurring in a patient under 10 years of age. The clinical course and therapeutic management of ESFT are also discussed.

Key words: Ewing's sarcoma – lung – MIC2

INTRODUCTION

Ewing's sarcoma family tumors (ESFT), which comprises Ewing sarcoma of the bone and primitive neuroectodermal tumors, is the second most common type of malignant bone tumor occurring in children and young adults, and it accounts for 10–15% of all primary bone tumors, following osteosarcoma (1). The annual incidence is estimated to be 0.6 per million population (2).

Most ESFT occur in the bone. As opposed to osteosarcoma, flat bones of the axial skeleton are more commonly affected, while in long bones, ESFT tend to arise from the diaphysis rather than the metaphysis. ESFT can affect any bone but the most common sites are the lower extremities (3).

Histologically, ESFT is a malignant, small, round-cell tumor. A classification scheme has been proposed for the differential diagnosis of ESFT based on the recognition of neural differentiation and characterized by the presence of Homer wright rosettes and/or immunohistochemically by the expression of at least two different neural markers (4). In addition, the glycoprotein p30/32 (CD99), which is encoded by the MIC2 gene, is strongly expressed on the surface of the tumor cells (5,6).

The identification of a non-random t(11;22)(q24;q12) chromosome rearrangement has been recently reported (7,8) in these aggressive malignant tumors, and this is considered to be strong evidence for their common histogenesis, while it is also a valuable characteristic that is useful in making a differential diagnosis from other small round cell tumors occurring in childhood and adolescence.

Cases of ESFT of the lung have been reported in recent years but there are very still few reports of primary pulmonary ESFT. To date, only eight cases of ESFT of the lung have been reported in the literature. Both the clinical course and the therapeutic management of this disease are discussed.

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CASE REPORT

An 8-year-old boy was admitted to a regional hospital because of a low-grade fever and non-productive cough. His past and family history were noncontributory. The findings of physical and laboratory examinations on admission were normal with no evidence of lymphadenopathy, but a chest X-ray demonstrated a large consolidation in the right lung (Fig. 1). A computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed a contrast-enhancing mass lesion in his right upper lobe of the lung (Fig. 2). The patient underwent a needle biopsy which revealed a proliferation of malignant small, round cells. As a result, he was transferred to our hospital to receive further treatment. A histological examination of hematoxylin–eosin stained sections showed a homogeneous population of closely packed small neoplastic cells with fibrovascular stroma. Most of the individual cells had scanty cytoplasm and round or oval nuclei with fine powdery chromatin (Fig. 3). A panel of immunohistochemical staining was performed. The tumor cells were strongly positive for CD99/MIC2 (Fig. 3) and negative for leukocyte common antigen, myoglobin, desmin, epithelial membrane antigen, AE1/AE3 and synaptophysin. CD99/MIC2 stain exhibited strong membranous staining. The histological and immunohistochemical findings were compatible with ESFT. We could not perform reverse transcriptase-polymerase chain reaction to detect EWS associated chimeric mRNA, such as EWS-FLI1, because the biopsied specimen was too small to do so. The patient thereafter underwent abdominal, pelvic and cervical CT, a whole body technetium bone scan, a gallium scan and a bone marrow biopsy, in addition to chest CT. As a result, neither any evidence of another tumor that could be associated with the primary site nor distant metastasis was observed.

Figure 1. Chest X-ray film showing a relatively circumscribed mass in the right lung.

After making the diagnosis, the patient was treated with neoadjuvant and adjuvant chemotherapy, including ifosfamide, etoposide, vincristine, doxorubicin and cyclophosphamide, and surgery. The histological examination of the resected specimen after chemotherapy revealed an

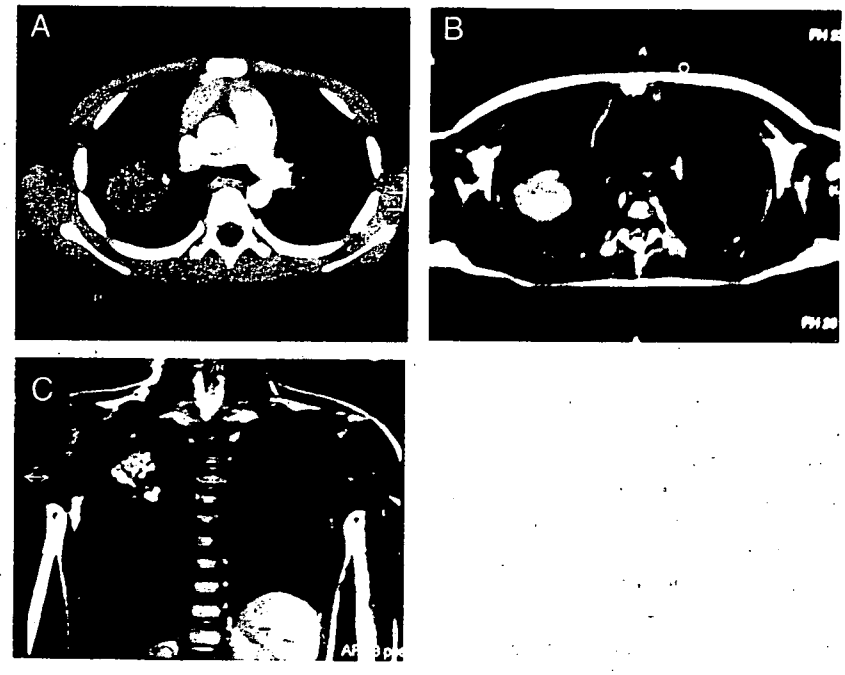

Figure 2. Computed tomography (A) and magnetic resonance imaging (B, C) demonstrate a lobulated mass confined to the lung parenchyma.

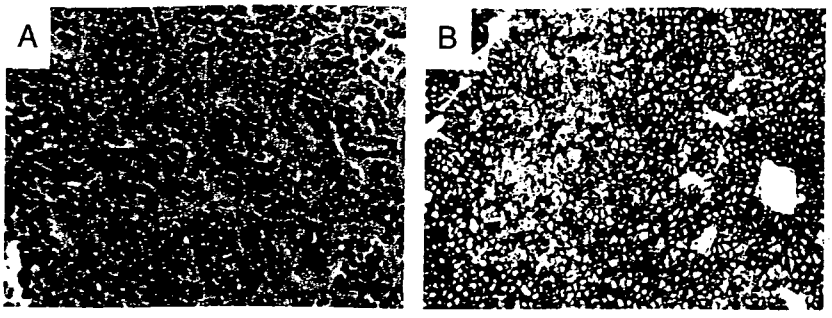

Figure 3. Primary Ewing's sarcoma family tumor (ESFT) of the lung. Microscopic features characterized by diffuse sheets of small round cells (A). Neoplastic cells showing distinct membranous reactivity for MIC2 (B).

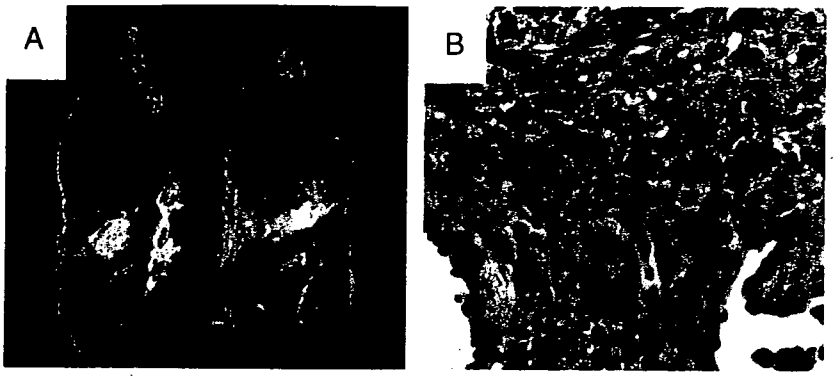

Figure 4. The cut surface of the lobectomy specimen showing a medullary tumor confined to the pulmonary parenchyma (A). A histological examination of hematoxylin–eosin stained sections showed small round neoplastic cells (B). The residual tumor was positive for MIC2 (not shown).

incomplete disappearance of the tumor cells (Fig. 4). Nine months later, after surgery, he is in good condition and chest CT scans reveal no evidence of recurrence.

DISCUSSION

The ESFT is an uncommon malignant neoplasm. The family shares a common histological feature of closely packed small primitive round cells. ESFT most frequently arise in the bones followed by the soft tissue, but they have also rarely been reported at other sites, such as the ovaries, uterus, kidney, pancreas, colon, hard palate and lung (9–20). The morphological features of the present intrapulmonary tumors were closely similar to those of ESFT observed at a variety of other locations.

The histologic differential diagnoses comprised other small, round cell malignancies, including malignant lymphoma, embryonal rhabdomyosarcoma and neuroblastoma. Immunohistochemical and histochemical staining positive for glycogen (PAS, 80%), neuron-specific enolase (60%), S-100 protein (50%) and MIC-2 marker (90%) as well as negative findings for leukocyte common antigen, epithelial membrane antigen, cytokeratin, desmin, vimentin, myoglobin and glial fibrillary acidic protein all indicate a diagnosis of Ewing sarcoma (21). In our case, both the histological and immunohistochemical findings were compatible with ESFT, whereas a genetic analysis could not be performed due to the insufficient amount of the biopsy specimen.

In this report, we describe a primary ESFT of the lung, bringing the total number of reported ESFT described at this site to nine cases, including the present one. The clinical features of these cases are summarized in Table 1. The median age was 27.6 (8–64) years, including six males. Four out of nine cases occurred in adolescents.

They were treated with various combinations of surgery, chemotherapy and radiation therapy. Of the seven patients with a follow-up, three were treated with surgery and chemotherapy and are still alive without disease at 16 months, 22 months and 2 years, respectively, after surgery. On the other hand, two patients treated by surgery died due to widespread metastatic disease 2 years after the operation. Based on this small number of cases, ESFT of the lung is thus considered to be an aggressive neoplasm that has a clinical course similar to ESFT occurring in other organs. In general, patients who present with metastases at diagnosis have a 5-year survival rate of 20–30%. The treatment of choice is an early surgical removal with intensive chemotherapy and radiation therapy to ablate any residual microscopic disease.

In summary, we herein described an extremely rare case of ESFT of the lung which demonstrated immunoreactivity to the MIC2 gene product. This is the first report of an ESFT

Table 1. Previous reports of primary Ewing sarcoma family of tumors of the lung

Reference	Year	Age	Gender	Metastasis at diagnosis	Treatment	Follow-up
Hammer et al.	1989	64	M	?	Ope/Chemo/RT	NE
Catalan et al.	1997	29	M	Multiple pulmonary nodules	Ope/Chemo	NE
Tsuji et al.	1998	25	F	None	Ope	DOD, 2 years
		15	M	None	Ope/Chemo	NED, 2 years
Imamura et al.	2000	41	M	None	Ope/Chemo	NED, 22 months
		30	F	None	Ope/Chemo	NED, 16 months
Kahn et al.	2001	18	M	None	Ope	DOD, 2 years
Mikami et al.	2001	18	F	?	Ope/Chemo/RT	DOD, 3 months
Present case	2006	8	M	None	Ope/Chemo	NED, 8 months

Ope, operation; chemo, chemotherapy; RT, radiotherapy; NE, not evaluable; DOD, dead of diseases; NED, no evidence of disease.

of the lung occurring in a patient under 10 years of age. In addition, we also reviewed the eight cases of primary ESFT of the lung previously reported in the literature along with the present case. The optimal treatment of primary ESFT of the lung has not yet been clearly established. Adjuvant and/or neoadjuvant chemotherapy may thus be able to improve the treatment results in the future.

Conflict of interest

None declared.

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■ 特集　小児固形腫瘍の分子生物学（その 3）：最新の知見

Ewing 肉腫ファミリー腫瘍の分子生物学

大喜多　肇*

はじめに

Ewing 肉腫ファミリー腫瘍（Ewing's sarcoma family tumor：ESFT）は，小児や若年成人の骨軟部に好発する腫瘍であり，原発性悪性骨腫瘍のなかでは骨肉腫に次ぐ頻度とされている。本腫瘍群には Ewing 肉腫，peripheral primitive neuroectodermal tumor（PNET）が含まれる。両腫瘍は，元来，異なる腫瘍として報告されてきたが，共通する染色体転座と病理組織学的特徴により，現在では，同一の範疇に入る腫瘍と考えられている。本稿では，ESFT における融合遺伝子の病理学的あるいは臨床的な意義と腫瘍発生における生物学的な意義について概説したい。

Ⅰ．病理組織学的特徴

Ewing 肉腫と PNET では，小型類円形でクロマチンの増量した核と明るい細胞質を有する腫瘍細胞が，繊細な血管性間質を伴ってびまん性に増殖する。Ewing 肉腫はほとんど分化形質を示さない。一方，PNET では Homer-Wright 型の偽ロゼットがしばしば認められ，免疫組織化学的に neuron specific enolase や neurofilament などの神経系のマーカーの発現が認められる。しかしながら，同一の腫瘍内にほとんど分化形質を示さない Ewing 肉腫の組織像を示す部と，神経系の形質を示す PNET の組織像を示す部が混在することもあり，Ewing 肉腫，PNET を明確に区別することは困難なこともある。これらの腫瘍は，免疫組織学的には CD99（MIC2）が，びまん性に膜上に陽性となるのが特徴的である。CD99 は ESFT の感度の高いマーカーであるが，リンパ芽球性リンパ腫をはじめとする他の小円形細胞腫瘍においても陽性となることがあり，鑑別診断上，留意する必要がある。

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表　ESFT に認められる染色体転座と融合遺伝子

転座の核型	融合遺伝子	頻度
t(11;22)	*EWS-FLI1*	80%
t(21;22)	*EWS-ERG*	15%
t(7;22)	*EWS-ETV1*	まれ
t(17;22)	*EWS-E1AF*	まれ
t(2;22)	*EWS-FEV*	まれ
t(16;21)	*FUS-ERG*	まれ
t(2;16)	*FUS-FEV*	まれ

Ⅱ．分子遺伝学的特徴

ESFT の約 80%に特徴的な染色体転座 t(11;22) が存在し，転座による融合遺伝子 *EWS/FLI1* が単離された（表）[1,2]。さらに約 15%には t(21;22) に由来する EWS/ERG 遺伝子が存在する。この 2 つの融合遺伝子に加え，頻度は非常に低いが，*EWS/ETV1*, *EWS/E1AF*, *EWS/FEV* といった融合遺伝子が報告されている[3]。これらの融合遺伝子はいずれも 5′側が *EWS* 遺伝子（EWSR1, Ewing sarcoma breakpoint region 1）で，3′側が ETS family に属する転写因子であり，*EWS/ETS* 融合遺伝子とも呼ばれている。*EWS* 遺伝子の産物は，RNA 結合蛋白質と考えられ，類似した構造を有する FUS（fusion in malignant liposarcoma), TAF II 68 (TAF15, TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa）とともに TET family と呼ばれている。それぞれの融合遺伝子の産物には N 末端側

の transactivation domain が含まれている。一方，3′側の転写因子には ETS DNA binding domain が in frame で含まれるというのが共通した特徴であり，融合遺伝子は異常な転写因子として作用すると考えられている。さらに，近年，*EWS/ETS* 融合遺伝子に加え，TET ファミリーのメンバーである *FUS* 遺伝子と ETS ファミリーの転写因子による融合遺伝子（*FUS/ERG*, *FUS/FEV*）が報告されている。

Ⅲ. 遺伝子診断

ESFT の病理学的診断は，特徴的な病理組織学的形態と免疫染色（CD99 陽性，他の分化マーカー desmin，TdT などが陰性）によってなされるのが一般的であろう。しかしながら，ごく少量しか腫瘍成分が得られない場合や，免疫染色の染色性が不良の場合など診断に苦慮することが少なくない。このような場合，融合遺伝子の同定が確定診断を下すために重要となる。筋と神経への分化を示す biphenotypic sarcoma で EWS/FLI1 が，desmoplastic round cell tumor で EWS/ERG が検出されたとの報告があること，FUS/ERG が急性骨髄性白血病の一部で同定されるなど，*EWS*（あるいは *FUS*）*/ETS* 融合遺伝子は，ESFT に 100%特異的とはいえないものの，非常に特異性が高いと考えられており，病理組織学的な形態所見と組み合わせて診断を行うことにより，より正確な診断が可能と思われる。一方，頻度は低いものの，融合遺伝子が検出されないが病理学的には ESFT と考えざるを得ない症例も存在する。このような場合は，病理組織学的鑑別診断（リンパ芽球性リンパ腫や低分化型の滑膜肉腫など）を十分考慮したうえで，ESFT の診断を下すべきであろう。

ESFT の場合，EWS と ETS family の転写因子が，さまざまな exon の組み合わせで融合するサブタイプが存在する。このことから，RT-PCR 法で遺伝子診断する場合，融合遺伝子に由来する PCR 産物の長さが症例により一定ではなく，シークエンスによる塩基配列の確認が必要な場合もある。さらに，パラフィン包埋ブロックを用いた RT-PCR の場合，標的とする配列を 100 塩基程度に短くする必要があるため，それぞれのサブタイプに応じた PCR プライマーの設計が必要であり，まれなサブタイプの検出は現実的には困難である。

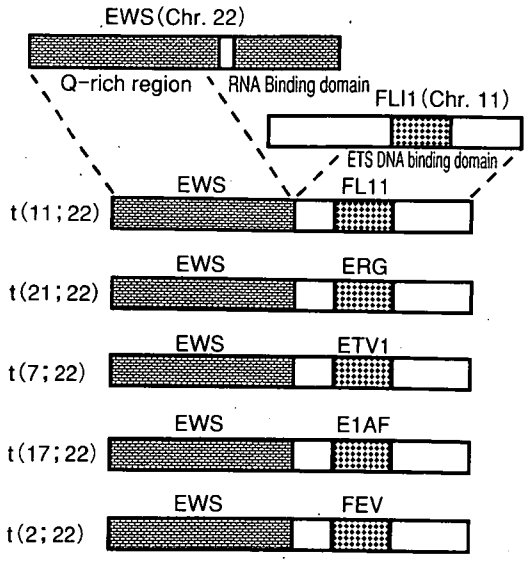

図 ESFT にみられる EWS 関連融合遺伝子の模式図

EWS の N 末端側には Q (glutamine)-rich region があり，FLI1 の C 末端側には ETS DNA binding domain がある。

各融合遺伝子のサブタイプと予後との関連については，差がないという報告もあるが，*EWS/FLI1* の type 1 とそれ以外の融合遺伝子を有する腫瘍では，前者のほうが予後が良いという報告もなされており，今後，さらに検討されるべき課題である[4]。また，骨髄や末梢血における融合遺伝子の検索によって微小残存病変を感度良く検出できると報告されているが，これらの臨床的意義の評価は現時点では定まっていない。

Ⅳ. 融合遺伝子による腫瘍発生機序

EWS/ETS 融合遺伝子は ESFT のほぼすべてに存在すること，*EWS/FLI1* は NIH3T3 をトランスフォームする能力を有することから，*EWS/ETS* は ESFT の腫瘍発生に非常に重要な役割を演じていると考えられている。*EWS/ETS* は，ETS DNA binding domain を有することから異常な転写因子として機能すると考えられており，その標的遺伝子が探索されてきた。これまで同定

された遺伝子のなかには，*c-Myc*（細胞周期やアポトーシスに関与するがん遺伝子）や CCND1 (cyclin D1，細胞周期関連分子)，PDGFC (platelet derived growth factor C，間葉系細胞に作用する増殖因子)，Nkx2.2（NK2 homeobox 2，神経細胞の分化にかかわるホメオボックスを有する分子)，NR0B1（オーファン核内受容体)，Id2 (inhibitor of DNA binding 2，bHLH 転写因子に対して抑制性に作用する分子）などが報告されている[5,6]。

また，融合遺伝子は転写を上昇させるばかりでなく，TGFBRII（TGF-βtype 2 receptor）や IGFBP-3（insulin-like growth factor-binding protein 3）のように融合遺伝子によって発現が抑制される分子も報告されている[7]。前述した分子に加えて，さまざまな培養細胞への融合遺伝子導入実験により，*EWS/ETS* 融合遺伝子の産物はかなり多数の遺伝子の転写を直接的あるいは間接的に制御していると考えられつつあり，ひとつの遺伝子の制御のみで腫瘍発生を説明することはできないようである。今後は，各標的分子が腫瘍発生に果たす役割を明確にするとともに，どの分子が腫瘍の発症，維持に重要であるか解明する必要があるであろう。

さまざまな培養細胞に融合遺伝子を発現させることによって，その腫瘍発生における役割が解析されてきた。マウスの線維芽細胞である NIH3T3 細胞が，*EWS/FLI1* の強制発現によりトランスフォームされ，ESFT の形質の一部が出現することが報告されている。また，*EWS/FLI1* の強制発現により神経芽腫や横紋筋肉腫に ESFT のマーカーが発現するなど，融合遺伝子はトランスフォーム能があるのみならず，細胞の分化形質も制御するものと考えられる。一方，ヒトの線維芽細胞に融合遺伝子を強制発現させてもトランスフォームされず，ESFT 様の形態変化も生じないようである。これらのことからヒトの細胞では融合遺伝子のみではトランスフォームに不十分で他の遺伝子異常なども必要と推測されるとともに，細胞の環境により融合遺伝子が発揮する効果が異なる可能性も考えられる。

一方，RNAi を用いて ESFT 細胞において *EWS/FLI1* をノックダウンすると，ソフトアガー上でのコロニー形成能が失われること，ヌードマウスでの腫瘍形成能が抑制されることが示された[5]。このことは，前述した強制発現の結果とあわせ，*EWS/FLI1* が ESFT にとって必須であることを示している。さらに，*EWS/FLI1* をノックダウンした ESFT 細胞の遺伝子発現プロファイルは，間葉系幹細胞に近づくこと，*EWS/FLI1* をノックダウンした ESFT 細胞は，脂肪や骨への分化能を示し，間葉系幹細胞様の性質が出現することが示された[8]。さらに，マウスの骨髄由来間葉系前駆細胞に *EWS/FLI1* を強制発現させると，ESFT 類似の腫瘍を形成しうることも報告された[9]。ESFT の発生母地は，未熟な間葉系細胞，神経堤細胞などの説が唱えられているが，これらの結果からは，間葉系幹細胞あるいはそれに近い細胞が ESFT の起始細胞であることが示唆される。今後，ヒト間葉系幹細胞/前駆細胞における *EWS/ETS* の機能が解明されることが期待される。

おわりに

融合遺伝子の発見以来，ESFT の疾患概念が整理されるとともに，その腫瘍発生における機能が盛んに研究されてきた。*EWS/FLI1* がある種の細胞に対してトランスフォーム能を有すること，ESFT 様の形質を与えることから，ESFT 発症において融合遺伝子が重要な役割を演じていると信じられているが，その作用機構にはいまだに解明すべき点が残されている。今後は融合遺伝子による ESFT 発症モデルの作製や，ESFT の起始細胞の同定，その起始細胞における *EWS/ETS* の機能解析が期待される。

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Molecular Biology of the Ewing's Sarcoma Family of Tumors

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Key words : Fusion gene, Ewing's sarcoma, Transcription factor, Molecular biology.
Jpn. J. Pediatr. Surg., 39(11) ; 1344～1347, 2007.

The Ewing's sarcoma family of tumors (ESFT) are bone and soft tissue sarcomas that occur in children and young adults. Specific chromosomal translocations found in ESFT cause EWS to fuse to a subset of ets transcription factor genes (ETS), generating chimeric EWS/ETS proteins. These proteins are believed to act as an aberrant transcriptional regulator and play a crucial role in the development of ESFT. The mechanisms responsible for the EWS/ETS-mediated tumorigenesis are well studied but remain uncertain. This review highlights recent advances in the molecular biology of ESFT.

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