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Enhancement of Metastatic Pulmonary Malignant Lymphoma Following Lung Irradiation

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放射線被曝肺組織へ転移が集中した悪性リンパ腫の症例

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31歳，女性の悪性リンパ腫の患者に両側鎖骨上窩，腋窩および縦隔へ予防照射を行ったところ，これによる被曝肺組織に悪性リンパ腫の転移を集中的に来たした症例を経験したので報告する．放射線被曝組織への悪性腫瘍転移が促進されるという実験的な報告は数多くなされている．しかし，悪性リンパ腫での臨床例の詳細な報告はみあたらない，又この原因についても諸説はあるが詳細は明らかでない．

The enhancement of metastases of malignant tumors in experimentally irradiated tissue has been well-documented[1)3)5)7)11)13)14)] However, unequivocal cases are rarely encountered clinically. Dao and Moore, and Dao and Kovaric reported dermal and pulmonary metastases in X-irradiated tissue of women post-mastectomy and postradiation therapy for breast cancer.[2)4)] This is a report of a case of malignant lymphoma with enhancement of pulmonary metastases following prophylactic irradiation of both supraclavicular and axillary regions, and the mediastinum.

Case Report

A 31-year-old female was admitted on June 18, 1971 with a chief complaint of left tonsillar and submandibular swelling. Biopsy of the left submandibular lymph node revealed malignant lymphoma

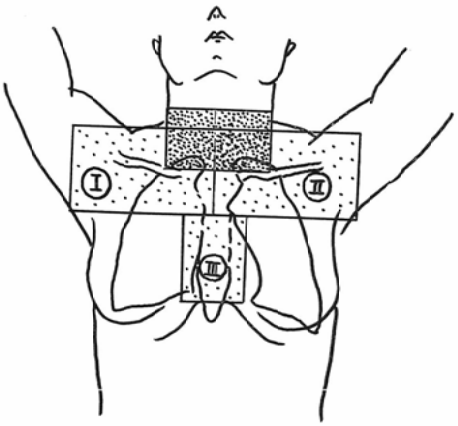

Fig. 1 Diagram of the prophylactic and neck irradiation fields. The lightly dotted area (I, II, III) shows the prophylactic irradiation of supraclavicular axillary region and mediastinum (I and II, opposing field, 10cm×20cm×2. III, opposing field, 16×9cm). The heavilly dotted area (inferior portion of the neck): Anterior field using 14 MeV electron beam, 8cm×8cm ×2.

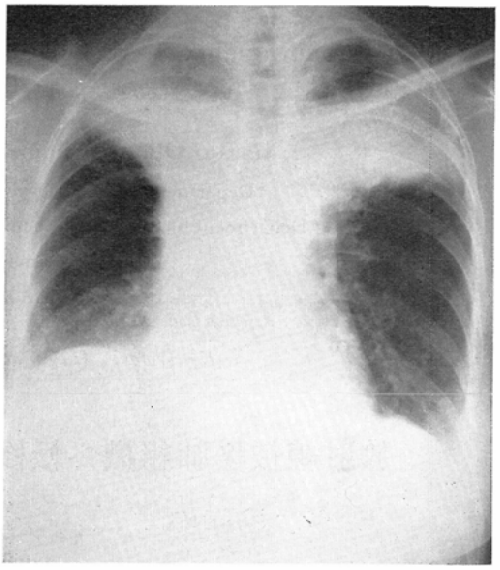

Fig. 3 The infiltrates became more denser after Oct. 27, 1971 and a right pleural effusion developed. (Dec. 9, 1971)

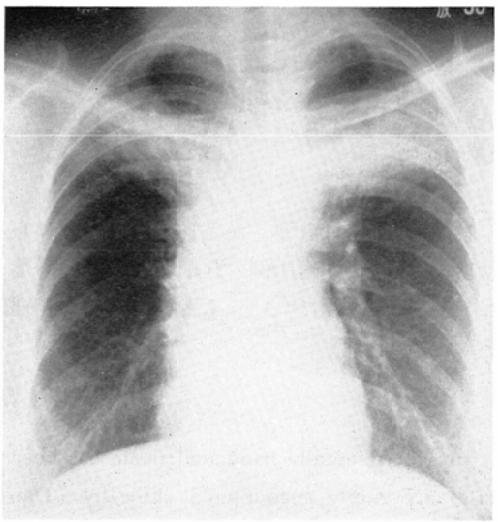

Fig. 2 Chest radiograph 2 months after completion of the initial radiation therapy shows bilateral infiltrates in the upper lobes and paramediastinal regions. The apices of both lungs are clear. (Oct. 27, 1971)

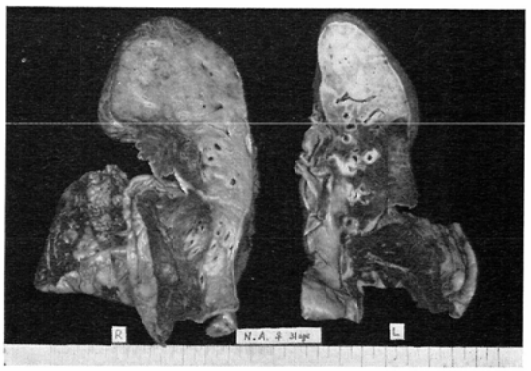

Fig. 4 Cut surface of the lung. Massive metastatic deposits were noted in the upper segments and paramediastinal regions of both lungs. The right paramediastinal region was more extensively involved than the left. Scattered foci of subpleural metastases were also observed.

(diffuse lymphoma, undifferentiated, non-Burkitt type). The tumor was limited to the left tonsillar and submandibular regions, and no other lymph nodes were involved. Chest radiography and bipedal lymphography were normal. From June 18, 1971 to Aug. 21, 1971, 5000 rad were delivered to the

tonsillar and submandibular regions, using a ^{60}Co-teletherapy unit, with lateral opposing 11 cm × 16 cm fields. There was marked regression of the tumor. On July 1, 1971 prophylactic irradiation of both supraclavicular and axillary regions and the mediastinum was begun, using 3 portals each anteriorly and posteriorly, and 200 rad daily 3 times weekly (Fig. 1). The lungs were not shielded. The prophylactic irradiation was completed on Aug. 21, 1971 with a total dose of 3000 rad. Chest radiography was normal at time of discharge on Aug. 25, 1971. On Sep. 21, 1971, the patient was readmitted with anterior neck tumor. Chest radiography on Sept. 29, 1971 was normal. 14 MeV betatron electron therapy via two anterior 8 cm × 8cm fields was administered to the neck with a total dose of 2800 rad from Oct. 7 to 26 (Fig. 1). The tumor did not regress and on Oct. 27, there was sudden onset of cough and dyspnea. Chest radiography revealed bilateral homogeneous infiltrates in both upper lobes and paramediastinal regions, apparently confined to the irradiation portals (Fig. 2). During the ensuing 3 weeks, the infiltrates increased in density and the patient became progressively dyspneic (Fig. 3). A pleural tap revealed malignant cells in a pleural effusion. The pleural effusion progressively increased until death. From Nov. 16, 1971 she received chemotherapy (VEMP; Vinblastin 4 mg × 4, Endoxan 100 mg × 44. 6 MP 50 mg × 44, Predonin 30 mg × 44), but her condition steadily deteriorated from disseminated disease and she died on Dec. 19, 1971.

Pathological Findings

Autopsy revealed generalized involvement of the lymph nodes and viscera by malignant lymphoma. The right and left lung weighed 520 and 720 g, respectively. The right lung was decreased in volume mainly due to a massive bloody pleural effusion (2000 ml). 300 ml of bloody pleural fluid was in the left pleural cavity.

The right and left pleural were mottled by metastases and hemorrhage. The cut surfaces of both lungs showed metastases confined to both upper lobes and the paramediastinal regions of middle and both lower lobes. The peripheral portions of the lungs were spared (Fig. 4). The metastic lesions were white, firm, lacked crepitance, and the margins of their intact portions were well-defined. Only the subpleural

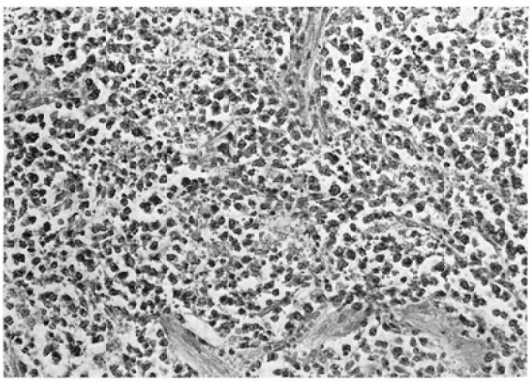

Fig. 5 A specimen from the upper lobe of the right lung shows that the lung tissue is replaced by lymphoma cells. (H & E ×200)

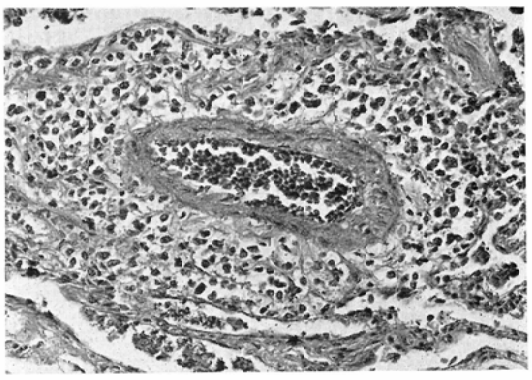

Fig. 6 A specimen from right upper lobe shows that at the periphery, tumor cells were spreading perivascularly. (H & E ×200)

regions showed evidence of tumor. The mediastinal and hilar lymph nodes were involved by metastases but there was no evidence of direct extension to the pulmonary tissue. Microscopically, both upper lobes and the paramediastinal regions were diffusely infiltrated with lymphoma cells (diffuse lymphoma, undifferentiated, non-Burkitt type) (Fig. 5). The alveolar spaces, filled with tumor cells, formed a uniform mass of tumor tissue. The tumor cells had spread perivascularly at the periphery of the growth (Fig. 6). Scattered fibrotic foci suggested radiation injury in both upper lobes and the paramediastinal regions Fig. 7). In both apices there was evidence of marked radiation injury with severe vascular and septal fibrosis (Fig. 8). The other deposits of lymphoma cells were confined to the subpleural regions. The other portions of the lungs were intact.

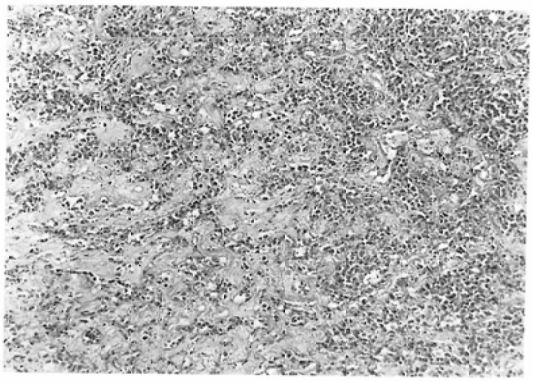

Fig. 7 A specimen from the upper lobe of the right lung shows fibrotic foci in the tumourous lesion suggestive of radiation injury. (H & E ×90)

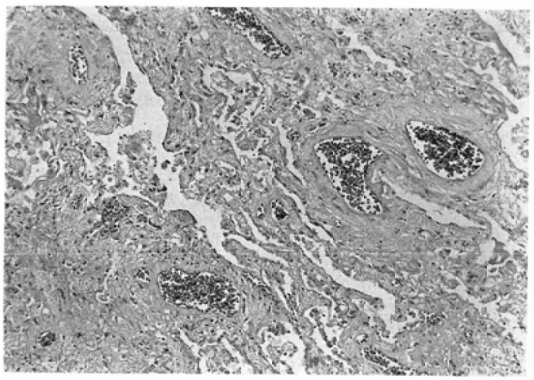

Fig. 8 The apex of right lung shows radiation injury with severe vascular sclerosis and septal fibrosis. There are no deposits of lymphoma cells. (H & E ×90)

Discussion

Secondary involvement of the lung in generalized malignant lymphoma is not uncommon. The tumor deposits are often confined to the subpleural regions but occasionally there is parenchymal involvement. Secondary pulmonary lymphoma is usually in the form of solitary or multiple nodular masses. Interstitial spread with-out mass formation is seen in some cases.

In the present case, there were massive parenchymal lymphoma cell deposits in both upper lobes and the paramediastinal regions. However, there was no evidence of direct extension of hilar or mediastinal lymphoma into the lung parenchyma. The pulmonary tumor cell deposits were symmetrically distributed confined to the irradiated areas, intermixed with fibrotic foci, and suggested radiation injury.

These findings strongly suggest that the irradiation enhanced the development of lung metastases in this case. The left paramediastinal region was less involved because this region was separated from the center of the portal by the heart.

Irradiation sensitization of an organ to metastases was experimentally documented for lung (Dao and Yogo, 1967; Fisher and Fisher, 1969; Zeidman and Filder, 1970, 1972; Brown and Phil, 1973; Tanaka, 1976) and liver (Koike, Nakazato, and Moore, 1963; Fisher and Fisher, 1969). Though there are numerous reports of experimental results, any literature contains no well-documented clinical case of this

in malignant lymphoma.

It is remarkable that the pulmonary lesions composed of tumor deposits and fibrotic foci suggesting radiation injury were mainly limited to the areas irradiated. We speculate that this unusual pulmonary spread of lymphoma cells was due to a local effect of irradiation on the lung tissue.

This effect may have been due to vascular changes such as dilatation of capillaries and increased permeability[8)9)13)] tending to decrease the velocity of blood flow and cause arrest of more tumor cell emboli in the pulmonary vascular bed.[5)12)] The work of Fisher indicated that vascular damage (trauma) favored the development of metastases in rats.[6)] It is also possible that an immunologic phenomenon may also have been active in our case.[1)2)]

The reason for the lung apices being spared from tumor invasion is not clear. However, the additional to the neck may have prevented this. No tumor cells were identified in the areas of microscopically severe pulmonary injury presumbly due to the high doses of irradiation (Fig. 8).

The dose to the lung, the time factor of irradiation, and the status of the disease seem important factors in causing such an unusual complication. The lung tissue must be damaged adequately for tumor cells to be viable to lodge, and for those adhering to the vascular walls to permeate extravasally.

Despite the many lymphoma cases treated with irradiation, we do not usually encounter such complications probably because the necessary conditions described do not often prevail and with proper timing. The present case is considered extremely rare because such precise conditions actually prevailed.

Although metastatic pulmonary malignant lympnoma enhanced by lung irradiation is rare and its mechanism is not clear, it is important and necessary to shield the lung tissue as much as possible to avoid this uncommon effect.

Acknowledgment

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