Malignant Lymphoma in an Atomic-bomb Survivor

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Atomic bomb survivors outside of Japan are few and often hard to follow-up. Spinal malignant lymphoma among these survivors is rare in established studies from Japan or the United States. Here, we report an 81-year-old woman, who experienced the atomic bomb explosion in Nagasaki when she was 19 years old, who presented with papillary thyroid carcinoma when she was 70 years old. Both follicular lymphoma over the right elbow region and vertebral malignant lymphoma were found when she turned 81 years old. Bone scan did not show any increased uptake of isotope. However, thoracolumbar spine magnetic resonance imaging showed multiple infiltrative soft tissue masses involving vertebral bodies at the T10–11 level. Computed tomography-guided biopsy further showed lymphocyte infiltration. Fortunately, the neurological deficit was improved after chemotherapy. The diagnosis of malignant lymphoma in atomic bomb survivors should be more careful and aggressive, even when their bone scan results show negative findings. In addition, the authors suggest that atomic bomb survivors should be followed-up carefully throughout their entire life. [*J Chin Med Assoc* 2009;72(7):388–393]

Key Words: atomic-bomb survivor, follicular lymphoma, malignant lymphoma, papillary thyroid carcinoma, radiation

Introduction

As time goes by, we have almost forgotten the atomic bombs that fell on Hiroshima and Nagasaki, Japan. The horror and sorrow of that time seem buried in the past. However, there remain many atomic bomb survivors in the world. According to data from the Radiation Effects Research Foundation (RERF) in Japan, more than 45% of this population was still alive in 2007.[1] They have a high risk of cancer and non-cancer disorders, and must face the possibility of radiation-induced cancer and non-cancer disorders every year. In this report, we present an 81-year-old woman with malignant lymphoma over T10–11 vertebrae with compression to her spinal cord and follicular lymphoma in the right elbow region diagnosed at the same time. She had had papillary carcinoma of the thyroid gland 11 years previously. The details of her clinical presentation, as well as the incidence and diagnosis of radiation-related cancers, will be discussed in this article.

Case Report

This 81-year-old woman was living in Nagasaki in 1945, when she was 19 years old. She claimed that she had not had any specific discomfort or any acute radiation-related disease since 1945 when the atomic bomb exploded in Nagasaki. The estimated dose of radiation she had received was <1 rad, because the distance from her work place to the site of bomb detonation was >2 km.[2] According to the latest RERF report in 2007, the incidence of solid cancer at the age of 70, if exposed at the age of 30, increased by about 58% per Gy for women.[1]

According to the patient's statement, she came back to Taiwan when she was 20 years old. Several decades later, when she was 65 years old, she began to receive regular follow-up in the special institute of Japan for atomic-bomb survivors. The examinations showed no significant abnormality until she was 70 years old. Unfortunately, thyroid gland enlargement was found incidentally by doctors in Taiwan. Fine needle aspiration

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was performed, and pathology showed papillary carcinoma of the thyroid, for which she underwent tumor excision. Due to residual tumor embedded in the great vessels and nerves, radioactive iodine (I^{131}) was prescribed. Tumor recurred when the patient was 77 years old. Surgical excision was performed, and a 1.5×2 cm nodule lesion was removed. Regular follow-up revealed no tumor recurrence and no distant metastasis.

However, when the patient was 81 years old, a firm but movable mass was found on the ulnar side of her right elbow region. Ultrasound showed a heterogeneous hypoechoic mass lesion, 2.9×1.7 cm in size, with hypervascularity (Figure 1). Although the tumor was attached close to the ulnar nerve, tumor removal was achieved uneventfully. Pathology showed malignant lymphoma with nearly total effacement of the nodal architecture by neoplastic follicles made up mainly of large cleaved cells. Grade 1 follicular lymphoma with predominantly follicular pattern was diagnosed (Figure 2).

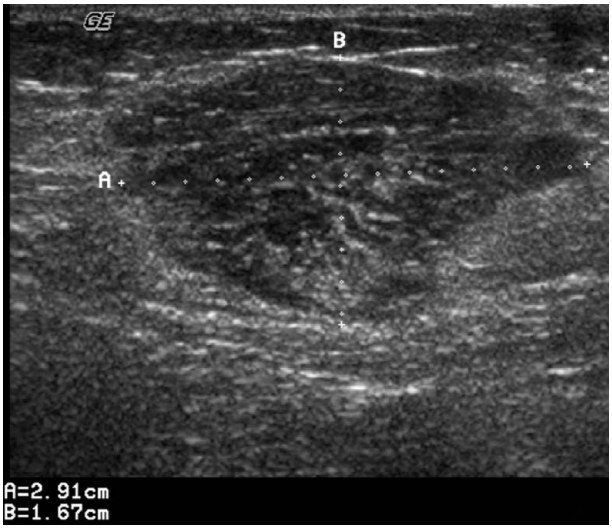

Figure 1. Ultrasound of the right arm region shows a heterogeneous hypoechoic mass lesion, 2.91×1.67 cm, medial aspect with hypervascularity.

At the same time, the patient also complained about back pain, especially at night, of several days' duration. Knocking pain was found over the T-spine area, with radiation to the buttocks and femoral region (T12 to L3 dermatome). No paresthesia or weakness (muscle power: 5/5) was found, but deep tendon reflexes of the left lower limb were mildly increased (+++). Due to suspicion of tumor, plain X-ray and bone scan were arranged. Except for degenerative joint change, there was no specific finding (Figure 3). There were also no hot spots on bone scan (Figure 4). Although the sensitivity of bone scan is high, we continued to suspect a spinal tumor because of the patient's clinical symptoms and signs. Therefore, thoracolumbar spine magnetic resonance imaging (MRI) with contrast enhancement was performed (Figure 5). There was an infiltrative soft tissue mass in the left paraspinal space of T10–11, involving the left T11 posterior vertebra, pedicle, neuroforamen, epidural space, spinal lamina, spinal process, and surrounding retrospinal space, encasing the spinal cord and causing spinal stenosis. The mass measured about $5.9 \times 4.1 \times 6.3$ cm in size. Moreover, there were para-aortic enlarged lymph nodes and mild compression fracture in T11. The radiographic images were compatible with spinal lymphoma.

Computed tomography-guided biopsy was done and showed diffuse infiltration of lymphoid cells associated with prominent germinal centers in a specimen of bone marrow of T11 vertebrae (Figure 6). The specimen of

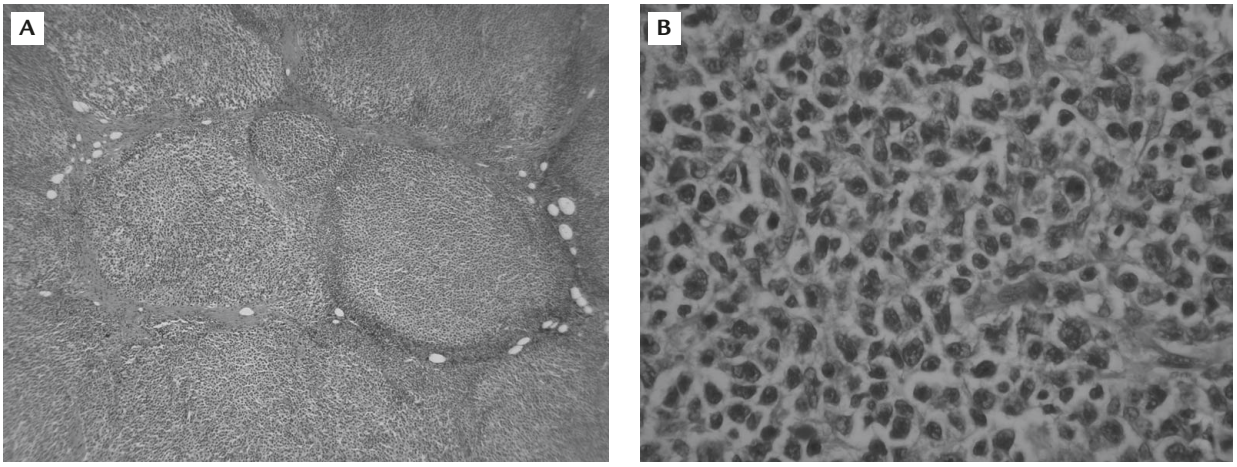

Figure 2. Surgical specimen from right elbow: pathology of grade I follicular lymphoma. (A) Malignant lymphoma with nearly total effacement of the nodal architecture, by (B) neoplastic follicles made up predominantly of large cleaved cells. Mean centroblasts are about 2/high power field.

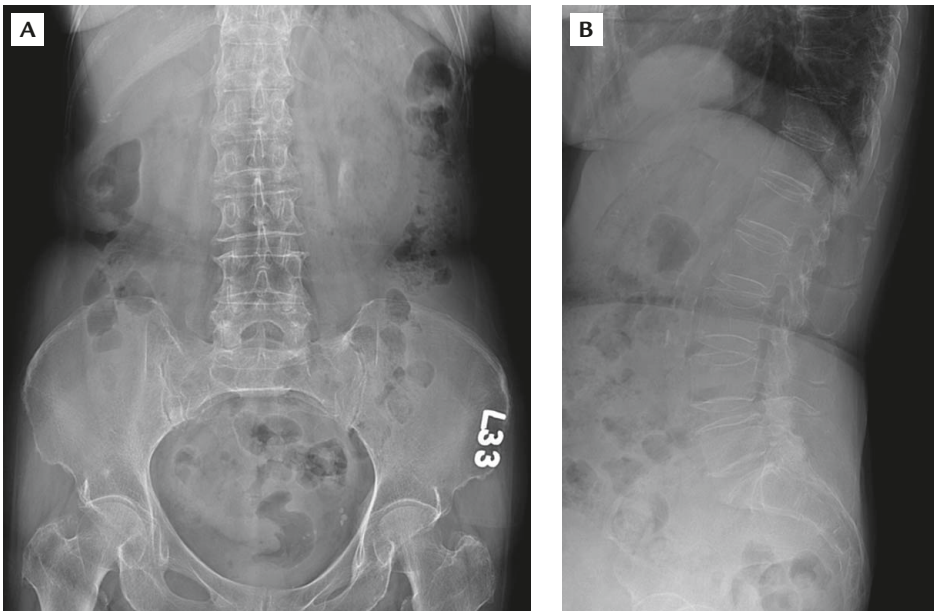

Figure 3. Plain X-ray shows mild osteoporosis and degenerative lumbar spondylosis but no evidence of vertebral bony erosion or other findings compatible with the patient's low back pain.

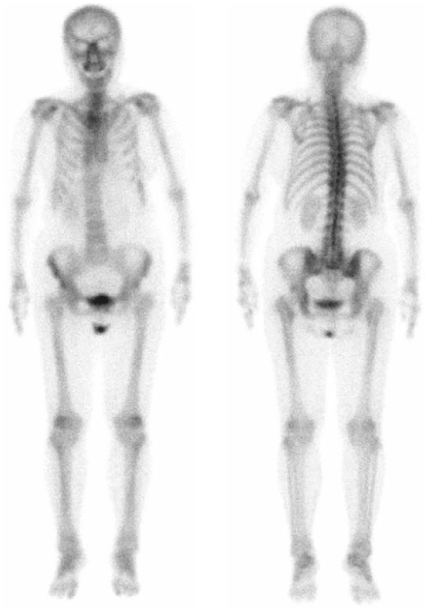

Figure 4. Whole-body bone scan performed 3 hours after intravenous injection of 15 mCi of Tc-99m-MDP. No abnormal focal bony uptake is seen.

paravertebral soft tissue showed only aggregation of small lymphocytes. The hematoxylin and eosin pattern of the specimen of bone marrow was like that of the specimen of right elbow lymphoma. Under the diagnosis of malignant lymphoma, the patient received 4-course chemotherapy of R-COP (rituximab, endoxan, oncovin, prednisolone). Adriamycin was not used due to its cardiotoxicity.

After 1-year follow-up, the patient's back pain and other discomfort had dramatically improved, and she could walk without any support. MRI revealed obvious regressive change in the tumor compared to the previous study.

Discussion

In the latest reports on mortality in the cohort of atomic bomb survivors followed-up by the RERF in 2003, the relative risks of cancer declined with increasing attained age (age at exposure + time since exposure).[3] In other words, those who were children when exposed have higher relative risks of developing cancer. A useful representative value of excess relative risk is given for those exposed at the age of 30—the solid cancer risk was elevated by 47% per sievert at the age of 70.[4]

According to the mortality data of the atomic bomb survivors in 1950–1985, there was an increase in cancers such as leukemia, lung, breast, esophagus, stomach, colon, ovary, urinary bladder, and multiple myeloma, but no increase in cancers of the rectum, gallbladder, pancreas, prostate, uterus, and malignant lymphoma. Again, sensitivity to radiation was higher among those who were younger at the time of the bomb explosion than among those who were older.[5]

Lymphomas are rarely found in this group of patients. In 1973, Nishiyama et al reported the prevalence of malignant lymphoma in these survivors,[2] who

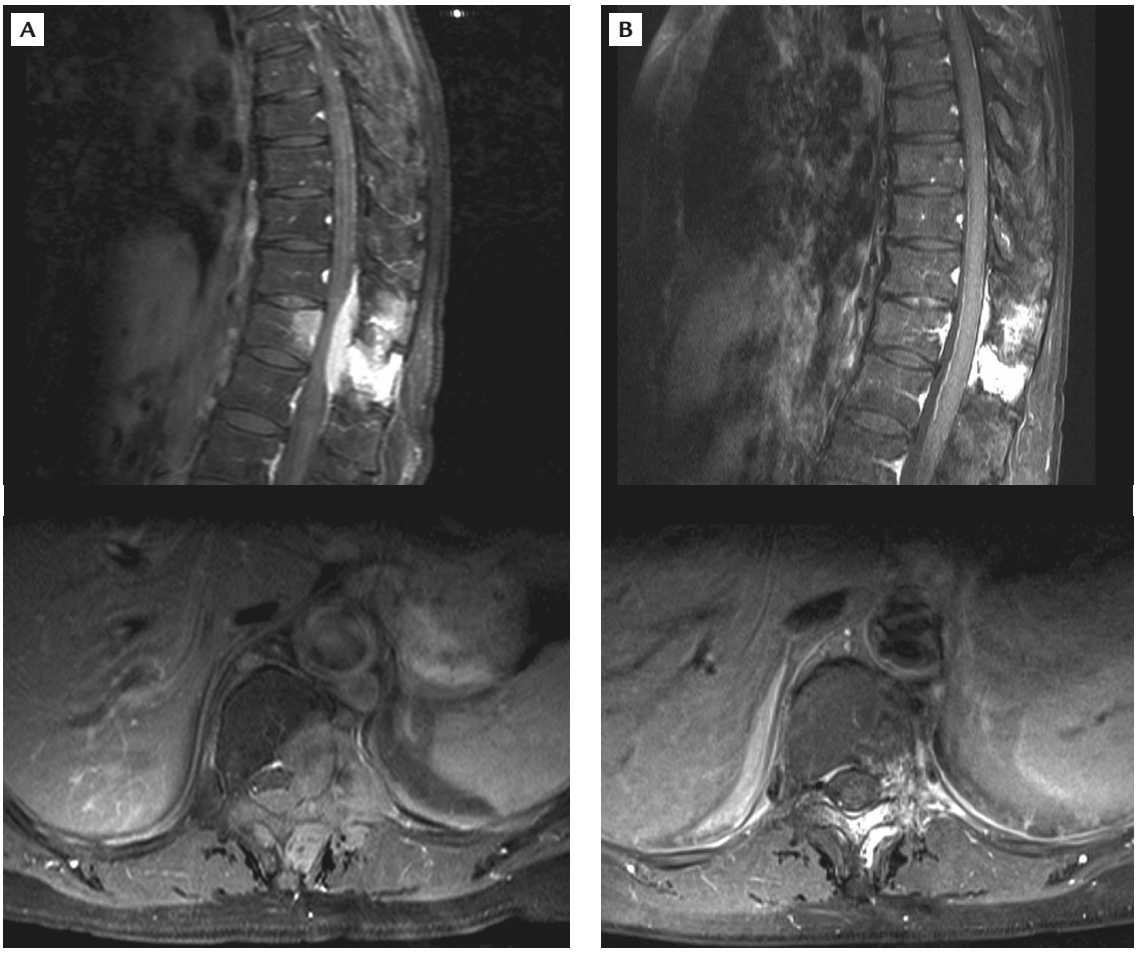

Figure 5. Magnetic resonance imaging of the thoracolumbar spine. Post-contrast sagittal and axial T1-weighted images with fat saturation. (A) Before chemotherapy: infiltrative soft tissue mass over the left paraspinal space at T10–11, involving the most critical structure of left T11. The mass is about $5.9 \times 4.1 \times 6.3$ cm in size, and mild compression fracture is seen in T11. (B) One year later, after chemotherapy, regressive change is seen.

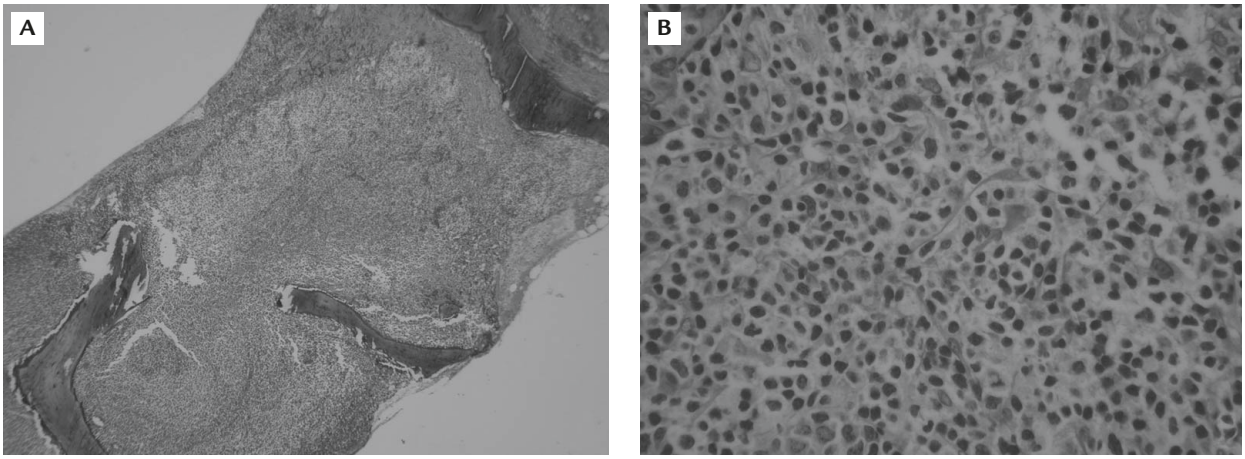

Figure 6. Pathology of atypical lymphoid cells from bone marrow of T11 vertebrae (from computed tomography-guided biopsy). The specimen is composed of: (A) bone fragments and bone marrow tissue with (B) diffuse infiltration of lymphoid cells associated with prominent germinal centers. The hematoxylin and eosin pattern of this specimen is like that of the lymphoma specimen from the right elbow.

were classified by 2 locations (Hiroshima and Nagasaki) and 3 subgroups (total dose: < 1 rad; 1–99 rad; ≥ 100 rad). Total dose was estimated by the distance from the hypocenter of the bomb. They found that the prevalences of malignant lymphoma were 3.47, 2.48 and 25.49 per 10,000 population in Hiroshima in the 3 subgroups, respectively. In Nagasaki, the prevalences were 7.95, 5.88 and 9.44 per 10,000 population in the 3 subgroups, respectively.[2]

In 1994, Preston et al presented an analysis of data on the incidence of lymphoma in the *Life Span Study* cohort of atomic bomb survivors during 1950 to 1987. That was the first analysis of the lymphoma incidence data of the cohort. A total of 229 lymphoma cases out of 93,696 survivors were identified. There was some evidence of increasing risk of lymphoma in males (excess absolute risk = 0.6 cases per 10^4 person-year sievert), but no evidence of any excess risk in females.[6]

Awa et al[7] and Kamada and Uchino[8] reported chromosome aberrations of T lymphocytes and bone marrow cells in atomic bomb survivors. Kamada et al also reported on the karyotypically abnormal clone of B-lymphocytes *in vivo*.[9] It is important for us to elucidate the processes of malignant lymphoma. Although many of the key mechanisms that explain how radiation induces human cancer (especially years after exposure) have yet to be determined, we now at least know for certain that radiation exposure indeed leads to breakage of double-strands in DNA, and causes defects in the DNA repair process. Extensive research is being carried out to identify which specific genes mutate in that repair process. Polygenic effects may play a role, and various single-nucleotide polymorphisms may, in combination, give rise to sufficiently dysregulated DNA repair, leading to predisposition to cancers.[10] This may well explain why some individuals who are exposed to radiation only develop single cancer, and why other patients develop multiple cancers.

Lyons et al reviewed the diagnosis of epidural malignant lymphoma.[11] Plain spine radiographic abnormalities have been reported in 15–42% of cases of spinal epidural lymphoma.[12–15] However, these reports were published before the advent of computed tomography, MRI, or other investigations.[12,13] In patients with secondary epidural lymphoma, spine radiographic abnormalities are detected in approximately 33% of cases.

There is no report about the sensitivity and specificity of bone scan in diagnosing epidural lymphoma. In general, the sensitivity of bone scan is high, while its specificity is low. In this case, initial radiography and bone scan did not show any abnormality. If MRI was not available, diagnosis and treatment would have been delayed. MRI or positron emission tomography may be required in atomic-bomb survivors who have severe back pain. Moreover, life-long regular physical examinations are needed in such patients.

Mascalchi et al reviewed the MRI findings of spinal epidural lymphoma in 8 patients.[16] The mean longitudinal extension of the epidural lesion was 2.6 vertebral segments. The tumors were homogeneously isointense with the spinal cord on T1-weighted images and isointense or hyperintense on proton-density and T2-weighted images. Diffuse signal changes in the vertebral body marrow consistent with osteolytic or osteoblastic changes were identified adjacent to or at a distance from the epidural lesion.

Our patient was exposed to radiation when she was 19 years old, but she was not too close to the site of bomb explosion. The histology was a rare follicular lymphoma, in contrast to the predominant types, including lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease, in Nishiyama et al's report.[2] In their report, the mean time to onset of malignant lymphoma was 12 years after bomb explosion. The 1-year survival rate was 45–58%, depending on histologic type (Hodgkin's disease > lymphosarcoma > reticulum cell sarcoma). Although we are unable to confirm whether our patient's malignant lymphoma was related to atomic bomb radiation, we did observe her excellent response to chemotherapy. As time goes by, slowly-growing malignant follicular lymphomas, like in this patient, require further study, data collection and analysis as these survivors age. Finally, we suggest that the diagnosis and management of epidural malignant lymphoma should be more careful and aggressive, even if bone scan results are negative, especially in patients with a history of radiation exposure.

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