CONCURRENT EPITHELIOID MALIGNANT PERIPHERAL NERVE SHEATH TUMOR AND PAPILLARY THYROID CARCINOMA IN THE TREATED FIELD OF HODGKIN’S DISEASE

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Abstract: Background. Simultaneous malignancies in the field of radiation for Hodgkin’s disease is an extremely rare event. A unique case of concurrent thyroid and neck mass in the postirradiation field of a young patient with Hodgkin’s disease is presented.

Methods and Results. Thyroidectomy and excision biopsy of the neck mass were performed. A 1.5-cm papillary thyroid carcinoma was identified in thyroidectomy and an initial diagnosis of undifferentiated malignant neoplasm was rendered on the neck mass biopsy. Subsequent surgical excision of the neck mass and immunohistochemical analysis revealed malignant peripheral nerve sheath tumor.

Conclusion. Concurrent malignancies in the field of treatment of Hodgkin’s disease may occur. Rare malignancies including malignant peripheral nerve sheath tumor may be encountered along with the more common papillary thyroid carcinoma.

Keywords: Hodgkin’s disease; postirradiation sarcoma; papillary thyroid carcinoma; peripheral nerve sheath tumor; epithelioid sarcoma

Modern radiation therapy techniques and the use of more effective combination chemotherapy regimens have resulted in the significant improvement of survival in adults and children diagnosed with Hodgkin’s disease. However, the subsequent development of second malignant neoplasms (SMNs) is an increasingly recognized cost of such success.1,2 The estimated cumulative incidence of second malignancy in children treated for Hodgkin’s disease is approximately 9.3% at 20 years.3 Most SMNs in this setting are solid tumors, with a cumulative incidence of 5.9% reported in 1 series; breast, thyroid, and skin cancers develop most frequently.3 Sarcomas are also common SMNs diagnosed in patients who have received prior radiation therapy, including those treated for Hodgkin’s disease.

Sarcomas are also not uncommon SMNs in patients with prior radiation therapy, including those treated for Hodgkin’s disease.4,5 Malignant peripheral nerve sheath tumors rarely occur in
the head and neck region,\textsuperscript{6–11} and the few that are diagnosed are usually associated with type 1 Neurofibromatosis de novo appearance is highly unusual.\textsuperscript{5–10} While there are several reports of bone or soft tissue sarcomas arising in patients previously treated for Hodgkin’s disease,\textsuperscript{4,5} these sarcomas are rarely neural in origin. Concurrent malignancies in postirradiation patients with Hodgkin’s disease are extremely rare. Only a few reported cases of such an occurrence have been published.\textsuperscript{12,13}

We report a case of a patient with synchronous SMNs, malignant epithelioid peripheral nerve sheath tumor and papillary thyroid carcinoma, in the irradiation field for Hodgkin’s disease.

\textbf{CASE REPORT}

A 34-year-old African American woman was initially seen in 1990 at the age of 18 with stage IA mixed cellularity Hodgkin’s disease. A full staging evaluation revealed disease confined to the right neck including a supraclavicular node. She was treated on protocol and received 3 cycles of NOVP (mitoxantrone, vincristine, vinblastine, and prednisone) chemotherapy followed by radiation to a mantle field. The treatment was planned to 40 Gy, but she received 24 Gy in 12 fractions due to her relocation during therapy and failed to complete the radiation as prescribed. She subsequently developed an abdominal recurrence of Hodgkin’s disease and received 6 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy without any consolidative radiation therapy.

In 2002, while undergoing a head and neck examination to evaluate enlarged tonsils, she was noted to have a left vocal cord paralysis. Radiographic examinations including CT scans of the neck and chest were performed to investigate the etiology of the vocal cord paralysis. A CT scan of the neck revealed a 2-cm mass in the left inferior carotid sheath with a central area of necrosis, extending from the inferior thyroid lobe to the superior mediastinum (Figure 1). An ultrasound performed to further evaluate the neck mass also revealed a well-defined, slightly hypoechoic solid nodule of the right thyroid. A fine-needle aspiration (FNA) of the left neck mass was unsuccessful due to patient complaint of a sharp shooting pain whenever the needle entered the mass, a clinical finding suggestive of a neuroma. Cytology of the right thyroid nodule revealed a papillary thyroid carcinoma.

The patient underwent total thyroidectomy and left neck exploration with excisional biopsy of the left neck mass in December 1992. Pathologic examination of the thyroidectomy specimens revealed a 1.5-cm papillary thyroid carcinoma within the right thyroid lobe (Figure 2). The biopsy of the left neck was diagnosed as an undifferentiated WHO grade 3, nasopharyngeal carcinoma presumably metastatic from a primary site in the head and neck. Subsequently, the patient underwent an examination under anesthesia with direct laryngoscopy and biopsy and bilateral tonsillectomy on January 2003 to try to localize the primary source of the presumed metastatic carcinoma. Pathologic examination of base of tongue, tonsil area, and nasopharynx showed no evidence of tumor. The patient received postoperative radioactive iodine therapy and thyroid hormone replacement for management of the thyroid carcinoma. The initial diagnosis neck mass was undifferentiated WHO grade 3, nasopharyngeal carcinoma presumably metastatic from a primary

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\caption{CT scan of the neck (A) and superior mediastinum (B) showing simultaneous papillary thyroid carcinoma (black arrow) and epithelioid neurosarcoma (white arrow).}
\end{figure}
site in the head and neck region. The patient underwent an examination under anesthesia with direct laryngoscopy and biopsy and bilateral tonsillectomy 6 months later in search of the head and neck primary. A pathologic examination of biopsies from the base of tongue, tonsil area, and nasopharyngeal tissues revealed no evidence of malignancy.

Further pathologic and immunohistochemical characterization of the left neck mass raised the possibility that the tumor could represent a peripheral neuroectodermal tumor. Repeat CT scans in April 2003 showed no change in the left neck mass; it measured 2.5 mm in greatest diameter and had some central necrosis. The patient refused chemotherapy and therefore underwent surgical resection via a left neck dissection and median sternotomy in June 2003. The mass encompassed the left vagus nerve and extended deep into the mediastinum.

**Pathology Findings.** The resected specimen revealed an 8.0- × 3.0- × 2.5-cm well-encapsulated, firm, fusiform mass involving the entire length of the left vagus nerve. The cut surface of the tumor was homogeneous and light tan in color, and showed no evidence of necrosis.

The histologic appearance of the tumor varied greatly from area to area. Some areas of the tumor appeared to be made of polygonal or round epithelioid cells arranged in a vague nodular pattern. These cells often had abundant eosinophilic cytoplasm and round nuclei with prominent nucleoli. In other areas, the tumor consisted of a proliferation of spindle cells that, on occasion, appeared to be arranged in poorly formed fascicles. Most of these cells had scanty cytoplasm and oval nuclei with finely granular chromatin and inconspicuous nucleoli. Mitotic figures were frequently seen in both the epithelioid and the spindle cell areas. Cystic degeneration and/or necrosis were absent.

The immunohistochemical examination was performed using the avidin–biotin–peroxidase complex (ABC) method with appropriate positive and negative controls. The antibodies (Dako, Carpenteria, CA) used were keratin CAM 5.2, neurofilament protein 2F11, desmin D33, HMB-45, and S-100 protein. Diffuse strong reactivity for S-100 protein was observed in the epithelioid areas of the tumor, while only rare spindle cells were...
positive. The staining for this marker was both nuclear and cytoplasmic. Focal positivity for neurofilament protein was present in both the epithelioid and spindle cell areas of the tumor, whereas sparse keratin reactivity was observed exclusively in the epithelioid areas. No reactivity for HMB-45 or desmin was seen.

Follow-Up. The patient remained asymptomatic, but repeat imaging studies in December 2005 showed a left paratracheal mass, a left internal mammary chain node, and a nonmetabolically active new 8-mm nodule in the right lower lobe of the lung. A FNA of the left neck mass revealed a malignant neoplasm consistent with the patient’s history of sarcoma. Immunostaining showed the tumor cells to be weakly reactive for antineurofilaments antibody in the left thyroid bed.

The patient received 4 cycles of vincristine, adriamycin, and ifosfamide, and then gemcitabine and taxotere due to the side effects. After 4 courses of this new regimen, she has had complete resolution of the lung nodules and stable disease in the neck.

DISCUSSION
In our case, the patient developed secondary papillary thyroid carcinoma and malignant epithelioid peripheral nerve sheath tumor 12 years after radiotherapy and chemotherapy. This highlights that as the cure rates for patients with Hodgkin’s disease have improved, the long-term treatment sequelae of developing SMNs has been increasingly recognized. In the 1380 children with Hodgkin’s disease reported by The Late Effects Study Group, 9.3% developed second neoplasms; 5.9% were solid tumors at 20 years. In a study of 196 patients with stage I Hodgkin’s disease who were treated predominantly (74%) with radiotherapy alone, Vlachaki et al reported that 10 and 20 years actuarial incidence rates of second malignancies were 8.1% and 16.7%, respectively. Because of the inclusion of nonmelanoma skin cancer and the differences in radiotherapy dose, fields, and chemotherapy regimens, a higher second malignancy incidence was reported than those by The Late Effects Study Group.

In the present case, the development of thyroid cancer after radiation and chemotherapy is in agreement with previous studies. Thyroid cancer is the second most common solid tumor reported among survivors of Hodgkin’s disease. The Late Effect Study Group reported a 36-fold increased risk of thyroid cancer, with 95% of these cancers developing within the radiation field. In the same study, of those patients who developed thyroid cancer, 69% received radiation and chemotherapy compared with 26% who received radiation alone. Green et al reported a 7.5% cumulative risk of having thyroid carcinoma at 30 years after treatment for Hodgkin’s disease.

To our knowledge, this is the first documented case of the development of an epithelioid malignant peripheral nerve sheath tumor in the head and neck region and in a patient with postradiation Hodgkin’s disease. The histogenesis of this entity is a subject of debate, but an origin from nerve sheath, Schwann cell, perineural cell, or fibroblast has been suggested. Epithelioid malignant peripheral nerve sheath tumor is an unusual subtype of malignant peripheral nerve sheath tumor (MPNST) that manifests morphologic features similar to those tumors of epithelial lineage. This variant accounts for approximately 5% of MPNSTs; they differ from conventional MPNSTs in that they are rarely associated with neurofibromatosis type 1 and they almost invariably express S-100 protein.

Because of their epithelioid features, the strong expression for S-100 protein, and the occasional positivity for keratin, epithelioid malignant peripheral nerve sheath tumors may be confused with both melanomas and carcinomas. The demonstration of a close association with a nerve, the negative staining with the HMB-45 antimelanoma antibody, and the presence of areas exhibiting a more conventional morphology allows, as in the present case, the correct diagnosis to be reached. The incidence of radiation-associated sarcoma is less than 1% in the literature. A combined study of 849 cases by Chrobowski et al and The Late Effect Study Group’s study of 1380 cases of Hodgkin’s disease reported only 10 sarcomas, none of which were MPNSTs (4 soft tissue sarcomas and 6 osteosarcomas).

Radiation-associated sarcomas generally pursue a worse clinical course than de novo sarcomas. Kim et al analyzed the results of over 300 patients with malignant nerve sheath tumors and reported a 61% death rate related to this disease. A report of a case of a postirradiation nerve sheath tumor in the spine for Hodgkin’s disease has also fatal outcome as patients with radiation-induced neural sarcomas. Malignant peripheral nerve tumors are best managed by surgery with or without adjuvant radiotherapy or chemotherapy. Complete resection and
negative margins are essential for local control and in this setting the expectation for local control 10 years from treatment is approximately 70%. In conclusion, this is an unusual case of a patient having 2 secondary tumors, of which 1 is a very rare presentation of epithelioid malignant peripheral nerve sheath tumor. At last follow-up, over 2 years out from diagnosis, her disease has been stabilized with surgery and systemic therapy, though the long-term prognosis remains guarded. As patients with Hodgkin's disease have high cure rates with modern radiotherapy techniques and new chemotherapy regimens, future investigations need to be directed at long-term effects of these therapies including prevention of secondary malignancies.

REFERENCES