Sarcoidosis mimicking metastatic thyroid cancer following radioactive iodine therapy

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Introduction: Sarcoidosis is an inflammatory disease characterized by non-caseating granulomas that can be present in diverse organ systems. Sarcoidosis can be associated with malignancy, presenting either preceding, during, or after chemotherapy. We herewith report a case of sarcoidosis mimicking cancer recurrence that developed after radioactive iodine therapy for papillary thyroid cancer.

Background: A 68-year-old Caucasian woman was found to have an incidental mediastinal lymph node. She underwent biopsy, which revealed sarcoidosis. There was no further treatment or evidence of recurrence over the ensuing 9 years. She was then diagnosed with low-grade papillary thyroid cancer in the right posterior lobe and treated with total thyroidectomy followed by radioactive iodine therapy. Six months later, she was found to have elevated serum thyroglobulin. Post–remnant ablation scan showed increased tracer uptake in the bed of the thyroid. Though two thyroid ultrasound scans were negative, she was treated with I-131 for possible recurrence. She then developed right hip pain, prompting further investigation. Though a skeletal survey was negative, an 18-fluorodeoxyglucose positron emission tomography (PET) scan study revealed multiple hypermetabolic skeletal lesions in both humeri and the proximal left femur. In addition, hypermetabolic hilar and mediastinal nodes were noted. As widespread cancer metastasis was suspected, bone biopsy was performed, which showed non-caseating granulomas, consistent with recurrence of sarcoidosis.

Conclusion: Sarcoid lesions may mimic metastatic disease or recurrence in oncologic patients. Biopsy and histopathology examination should be performed to confirm the diagnosis. Recurrence or reactivation of sarcoidosis has been proposed to result from altered immunologic milieu because of the presence of either active cancer or its therapy. Teodorovic and colleagues postulated that the radioactive I-131 therapy leads to reduced secretion of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13. Few case reports of sarcoidosis associated with papillary carcinoma have been published; this is the first report of systemic recurrence of sarcoidosis associated with papillary thyroid carcinoma after treatment with radioactive iodine therapy.

Keywords: radioactive iodine therapy; papillary thyroid cancer; sarcoidosis; cancer metastasis; PET scan

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a free serum triiodothyronine (T3) of 3.3 ng/dl (normal 3.6–5.6 ng/dl), and a thyroid-stimulating hormone (TSH) of 0.226 mU/L (normal 0.5–5 mU/L). A thyroid ultrasound demonstrated a right upper pole nodule measuring 2.5 cm × 1.8 cm × 1.4 cm, a right mid-pole nodule measuring 1.3 cm × 1.1 cm × 0.8 cm, and another right mid-pole nodule measuring 1.5 cm × 1.0 cm × 1.1 cm. In addition, there was a nodule in the left upper pole measuring 1.4 cm × 1.0 cm × 0.5 cm and a nodule in the left lower pole measuring 1.5 cm × 1.1 cm × 1.0 cm. Needle biopsies of the right upper pole and mid-pole nodules both demonstrated benign cytology. A thyroid scan showed normal uptake. She was diagnosed with multinodular goiter with subclinical hyperthyroidism and treated with methimazole for several months. Follow-up TFTs 1 year later showed TSH of 0.356 mU/L (normal 0.5–5 mU/L), T4 of 0.85 ng/dl (normal 0.9–2.4 ng/dl), and T3 of 133 ng/dl (normal 3.6–5.6 ng/dl).

Her TSH was 0.11 mU/L (normal 0.5–5 mU/L) 1 year later, prompting another thyroid ultrasound. The previous nodules were unchanged, with the exception of the two hypoechoic nodules on the right lower pole, measuring 1.2 cm × 1.2 cm × 1.2 cm, and a right posterior hypoechoic nodule with a calcified rim measured 1.0 cm × 1.2 cm × 1.3 cm. A fine needle aspirate of the right posterior nodule was consistent with low-grade papillary cancer (Fig. 1).

She then underwent total thyroidectomy, and on surgical pathology, the cancerous lesion was 1.2 cm × 1 cm and locally invasive to the cricoid cartilage and the capsule. The patient then received 102.5 mCi of I-131 and suppressive therapy with high dose levothyroxine.

TFTs 6 months after treatment showed TSH of 0.027 mU/L (normal 0.5–5 mU/L), free T4 of 1.62 ng/dl (normal 0.9–2.4 ng/dl), thyroglobulin of 73 ng/ml (Ref range: 1.60–59.90 ng/ml), antithyroidperoxidase antibodies (Anti-TPO Ab) < 10 IU/ml (Ref range: 0.0–35.0 IU/ml), and antithyroglobulin antibody (Anti-TG Ab) < 20 IU/ml (Ref range: 0.0–40.0 IU/ml). A post–remnant ablation scan showed increased tracer uptake in the bed of the thyroid. Two thyroid ultrasounds, however, were negative. She was then treated with I-131 for a second time because of the increased tracer uptake. Her thyroglobulin level subsequently decreased to 10.70 IU/ml 3 months after this I-131 treatment. Her last TFTs 1 year after the second I-131 treatment showed TSH of 0.067 mU/L (normal 0.5–5 mU/L), T4 of 1.49 ng/dl (normal 0.9–2.4 ng/dl), Thyroglobulin of 0.91 ng/ml (Ref range: 1.60–59.90 ng/ml), and Anti-TG Ab of 20 IU/ml (Ref range: 0.0–40.0 IU/ml).

The patient was stable until 4 months later, when she developed right iliac crest pain. Evaluation at that time was not specific, aside from relative leucopenia, averaging 3.18–3.56 (normal 4,000–10,000/μl), 25-hydroxy vitamin D of 17 (normal 25–80 ng/ml), and 1,25-dihydroxy vitamin D of 50 (normal 25–80 ng/ml). Additional laboratory tests showed that her calcium was 9 (normal 9–10.5 mg/dl), ACE level 14 (normal < 40 μg/L), and ESR 26 (normal 0–20 mm/h). A skeletal bone survey was negative, but

Fig. 1. Typical nuclear features of papillary carcinoma, including nuclear inclusions (arrows) and grooves (arrowhead).
a positron emission tomography (PET) CT scan showed multiple hypermetabolic skeletal lesions in both humeri and the proximal left femur, and hypermetabolic hilar and mediastinal nodes (Figs. 2 and 3). Because of the high suspicion for metastatic disease, the patient underwent a bone biopsy of the femur lesion. The pathology showed non-caseating granulomas, consistent with osseous sarcoidosis (Figs. 4 and 5). It was suspected that thyroid cancer was the main stimuli for her recurrent sarcoidosis.

She has not received any specific sarcoid-directed treatment and remains cancer-free from the perspective of her thyroid cancer.

**Discussion**

Sarcoidosis is an inflammatory disease characterized by the presence of non-caseating granulomas. The disease often involves multiple organ systems and requires the involvement of two or more organs for a specific diagnosis (1).
Fig. 4. Low-power histological evaluation showed small fragments of bone marrow with a non-caseating granuloma with no evidence of malignancy (H&E, 10×).

Fig. 5. Higher power showed a non-caseating granuloma consistent with sarcoidosis (H&E, 40×).
Although sarcoidosis can affect virtually every organ of the body, lung involvement is the most common (1, 3). Other organ systems commonly involved are the liver, skin, and eyes (1, 3). Despite intense investigation, the cause of sarcoidosis remains elusive. Currently, the most popular proposed etiology is that an infectious or non-infectious environmental agent triggers an inflammatory response in a genetically susceptible host (3, 4).

The incidence of bone marrow manifestations in sarcoidosis is 7% (1). The most common hematologic complication is lymphopenia, which probably reflects sequestration of lymphocytes into areas of inflammation. Anemia occurs in 20% of patients and leucopenia is less common (1, 5). Bone marrow examination reveals granulomas in about a third of sarcoid patients. Both bone marrow and spleen involvement are more common in African-Americans than their Caucasian counterparts (1). These manifestations alone are rarely an indication for therapy. Our patient manifested bone pain and mild leucopenia, and the decision was made to monitor her symptoms conservatively.

A review of the literature suggests that the relationship between sarcoidosis and malignancy is controversial. Though new onset sarcoidosis or recurrent sarcoidosis has been reported in oncology patients (6–8), the exact mechanism inciting sarcoid activity remains elusive. It is possible that in our case, the thyroid cancer was unrelated and coincidental to the recurrence of her sarcoidosis. Yet, according to two retrospective case series, 4–14% of all patients with malignancy can exhibit some histopathological evidence of sarcoidosis (9, 10).

Cases of sarcoidosis either preceding or associated with malignancy have been published involving a wide variety of tumors: hematologic malignancies such as acute myeloid or lymphoid leukemia; Hodgkin’s disease; solid organ tumors such as breast, lung, liver, or digestive tract; gynecologic malignancies such as ovary, cervix, vulva, uterus; and other tumors such as melanoma and schwannoma (2, 11–13).

Several proposed mechanisms for the pathogenesis of sarcoidosis associated with malignancy exist. One hypothesis is that localized sarcoidosis may be related to degenerative and necrotic changes within the tumor itself and that systemic sarcoidosis may be mediated by humoral and T cell–mediated factors, with subsequent recruitment and activation of macrophages (9, 10, 14). Teodorovic et al. postulated that the radioactive I-131 therapy leads to reduced secretion of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 (15). Another hypothesis is that chemotherapy inhibits local immunological responses, thereby preventing granuloma formation and development of associated disease symptoms (16). Our case does not favor the latter mechanism, as it is unlikely that an immunosuppressive state can be solely attributed to radioactive iodine.

In clinical practice, radiographic abnormalities in cancer patients are often presumed to represent metastasis. Our case demonstrates the conundrum that the clinical presentation and radiological evaluation, including PET and CT scans, does not discriminate between cancer recurrence and sarcoidosis. Therefore, sarcoid or sarcoid-like reactions should be considered in the differential diagnosis of oncologic patients who have developed FDG-avid lesions any time after antineoplastic therapy. Histopathologic examination is necessary to confirm a definitive diagnosis.

### Table 1. Relationship between sarcoidosis and papillary carcinoma

| Authors            | Location of sarcoidosis       | Types of thyroid carcinoma | Newly diagnosed or recurrence sarcoidosis                              | Others association                                                                 |
|--------------------|-------------------------------|----------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Koshiyama H et al. | Right subclavian mass         | Papillary                  | Newly diagnosed sarcoidosis after thyroid cancer                      | Total thyroidectomy with radical neck dissection, but no I-131 had been given when sarcoid was diagnosed |
| Kuroda T et al.    | Regional lymph nodes (parathyroidal, pretracheal, right upper internal deep cervical, and submandibular lymph nodes) | Papillary                  | Newly diagnosed sarcoidosis after thyroid cancer                      |                                                                                  |
| Feldt-Rasmussen U et al. | Thyroid gland             | Papillary                  | N/A                                                                    | Developed cancer 2 years after thyroid sarcoid was diagnosed                      |
| Krzysztof Sworczak et al. | Thyroid gland            | Papillary                  | N/A                                                                    | Developed cancer after long-term treatment of minocycline                         |
| AHM Smelt et al.   | History of thyroid; cutaneous, pulmonary sarcoid | Papillary                  | N/A                                                                    |                                                                                  |
Conclusion
To our knowledge, this is a novel case of sarcoidosis that reoccurred following radioactive iodine therapy for papillary thyroid cancer. That sarcoidosis can mimic cancer metastasis is particularly vexing. Few case reports of sarcoidosis associated with papillary carcinoma have been published (Table 1), with this one being the first report of systemic recurrence sarcoidosis associated with treatment with radioactive iodine therapy. Unfortunately, PET scan does not distinguish between metastasis and sarcoidosis, mandating that biopsy and histopathology examination be pursued to obtain the correct diagnosis.

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