CASE 1. Langerhans Cell Histiocytosis of the Thyroid

A 46-year-old woman presented to her physician with an enlarging, painful neck mass, mild dysphagia, and right otalgia. Her other health problems included diabetes mellitus, hypertension, and dyslipidemia. She had been diagnosed with diabetes insipidus 15 years earlier after experiencing polyuria and polydypsia, and this disorder was controlled by desmopressin, 0.1 mg by mouth three times per day. Pertinent findings on physical examination were an asymmetrically enlarged and tender goiter (Fig 1). Thyroid panel was normal. Thyroglobulin level was elevated to 9,235 ng/mL (normal range, 1 to 40 ng/mL). Computed tomography scan of the neck revealed heterogeneous enlargement of both thyroid lobes with anterior lobulated projections (Fig 2A). There was no evidence of enlarged lymph nodes. Magnetic resonance imaging of the brain, nuclear bone scan, and chest computed tomography scan were normal. Attempted thyroidectomy was aborted because of a significant hemorrhage (2 L of blood) during the initial part of the surgery, but a biopsy of the thyroid gland was obtained. It demonstrated histiocytes (Fig 3, arrow) infiltrating the space between the thyroid lobules (Fig 3, star), with phenotypic features and immunohistochemical profile (positive for S100, CD1A, and CD68-PGM1) consistent with Langerhans cell histiocytosis (LCH). The patient was treated initially with interferon-alfa 1 × 10^6 units subcutaneously three times per week, for 4 months. This treatment was ineffective, as reflected by enlargement of the size of her goiter, worsening of the tenderness and dysphagia, and an increase in thyroid size on computed tomography scan. Subsequently, she was treated with two courses of cladribine, with initial response followed by progressive regrowth. The patient was then treated with pentostatin (2'-deoxycoformycin), a purine analog with adenosine deaminase inhibitory activity, at a dose of 4 mg/m² by intravenous infusion once every 2 weeks. The patient achieved a partial remission and continues to respond to this regimen 6 months (11 cycles) later, with ongoing shrinkage of her goiter (Fig 2B).

LCH is most commonly a pediatric disease, but it can affect the adult population. It usually presents as a multisystem granulomatous infiltrate (in two thirds of cases) in adults. Bone involvement predominates (80% of cases) with osteolytic and asymmetric lesions,
most often of the skull. Extraskeletal extension involves mainly the skin, the pituitary gland with diabetes insipidus, the liver and/or spleen, the lungs, and the orbits.2 Thyroid gland infiltration remains uncommon with about 34 cases (22 adults and 12 children) reported in the medical literature, the vast majority presenting as multisystem disease.3–6 Due to its rarity, diagnosing LCH of the thyroid can be challenging. It can be clinically confused with the far more common benign goiters, undifferentiated carcinoma, lymphoma, lymphocytic thyroiditis, and chronic granulomatous thyroiditis. In fact, LCH of the thyroid can both masquerade as a malignancy or coexist with another thyroid neoplasm. LCH of the thyroid has been misdiagnosed as papillary carcinoma,7,8 or anaplastic malignancy of the thyroid.9 Papillary carcinoma can also coexist with LCH within the thyroid gland,10 or within the lymph nodes draining the bed of a thyroid carcinoma.5,11,12 The key to diagnosis of LCH is to identify the pathologic Langerhans cells that resemble the normal Langerhans cells of the skin, except they are not dendritic in morphology (Fig 3). They do demonstrate a characteristic nuclear groove and positive immunostaining with CD68, S100, and CD1a.4–6 The course of LCH is often unpredictable, varying from spontaneous regression to aggressive progression and death. It is not uncommon (20% of cases with multisystem involvement) to witness a capricious course with repeated recurrence of the disease and considerable risk of permanent sequelae.13 Excluding LCH of the lung, which seems to be a separate syndrome, “multisystem” LCH disease has a worse prognosis than monofocal disease, with 10% to 30% mortality and a 50% risk of life-impairing morbidity. For aggressive disease, multiple chemotherapeutic regimens have been attempted: glucocorticoids, vinblastine, etoposide, cyclophosphamide, methotrexate, and doxorubicin. Recently, cladribine (2-deoxycoformycin), another purine analog antimetabolite, has shown promising responses in LCH.14 There are also anecdotal reports describing treatment of LCH with pentostatin (2-deoxycoformycin), another purine analog, which directly inhibits adenosine deaminase.15 Thyroidectomy has also been attempted with pentostatin (2-deoxycoformycin), another purine analog, which directly inhibits adenosine deaminase.15 Thyroidectomy has also been used with some success.3 Our patient demonstrated a 41% reduction in thyroid size after one course of cladribine, but the thyroid began to grow back with the second course. She was given pentostatin, which resulted in ongoing decrease in size after 11 courses and meeting criteria of partial remission with an overall 52% reduction in the size of the thyroid gland.

Fadi Braiteh and Razelle Kurzrock
Phase I Program, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, and the University of Texas Graduate School of Biomedical Sciences at Houston, Houston, TX

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CASE 2. Acquired Hypertrichosis: A Rare Paraneoplastic Syndrome in Various Cancers

A 62-year-old white woman patient presented with extremely dense hair growth in her face, arms, and on her back. The hair growth had started 6 months previously on the chin, gradually spreading over the whole face, arms, and back. Because of the abnormal hair growth, she did not leave her house. Her weight was unchanged for the last 3 years, and she did not take any medication the last 1.5 years. She also complained of a painful mouth, and had noticed blisters in her mouth. Menopause started on her 43rd year. On physical examination, her blood pressure was 140/70 mmHg, pulse 80/min (regular). Her weight was 80 kg, length 1.70 m, and body-mass index 27.7 kg/m2. No symptoms of Cushing’s disease were present. The dense hair growth consisted of 2-cm long, white, thin, soft hairs, prominently present on the face, arms, and back (Fig 1). Oral examination, as well as further examination, were unremarkable. On laboratory examination, serum testosterone, dihydrotestosterone, 4-androstenedione, dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and sex hormone-binding globulin were within the normal range; luteinizing hormone, follicle-stimulating hormone, and estradiol were within the normal postmenopausal range. Twenty-four-hour urinary cortisol secretion and 1-ng dexamethasone suppression testing was normal. On magnetic resonance imaging scan, the left adrenal gland contained a 1-cm lesion, suspicious for an adenoma. Because of the extreme hair growth, therapeutic measures were advised. Under the clinical diagnosis of hirsutism, the left adrenal gland was removed using minimal invasive surgery: it appeared to be a benign adenoma. During the same procedure, the adnexa were laparoscopically removed, and the left ovary unexpectedly showed metastases of a moderately differentiated adenocarcinoma, possibly from the colon. On colonoscopy, a stenosing tumor was found. Consecutively, a palliative resection of the right-sided colon was carried out. A tumor with a length of 7 cm was...