Case Report

Mycosis Fungoides and Head and Neck Malignancies

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Abstract Mycosis fungoides is a cutaneous T-cell lymphoma characterized by cutaneous patches and plaques that may progress to hematologic involvement and Sezary syndrome. Second primary tumors have been described in the literature without emphasis on head and neck neoplasms. We report two cases of head and neck malignancies in patients with a history of mycosis fungoides. A PubMed literature search was performed and results were reviewed. Second primary tumors in the head and neck have been reported in the nose and nasal cavity, sinuses, oral cavity, pharynx, hypopharynx, larynx, tracheobronchial tree, thymus, and skin. We present cases of submandibular mucoepidermoid carcinoma and papillary thyroid carcinoma in patients with a history of mycosis fungoides. Mycosis fungoides may confer increased risk of developing a second primary neoplasm of the head and neck. Possible mechanisms may include immunosuppression inherent in treatment modalities, the disease course of mycosis fungoides, or related genetic mutations.

Keywords mycosis fungoides; head and neck malignancies; second primary

1. Introduction

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma [29]. It was first described in 1806 by French dermatologist Jean-Louis-Marc Aliber [16] and typically affects adults between the ages of 55 and 60 and is twice as common in males than females [29]. The most recent age-adjusted annual incidence in the United States has been estimated to be 6.4 cases per 1,000,000 [17]. Clinical features of MF are varied depending on the stage and disease progression. Initial symptoms usually include skin changes, such as erythematous scaly patches or plaques that often resemble common skin conditions which can progress to generalized erythroderma (Figure 1). Patients often describe intense pruritis. Infrequently cutaneous lesions may progress to ulcerated or exophytic tumors. Lymphadenopathy is also well-described as a late occurrence. Patients with advanced disease may develop visceral dissemination, and the most commonly involved organs are the lungs, spleen, liver, gastrointestinal tract, kidneys, thyroid gland, pancreas, bone marrow, and heart [16,29]. MF has also been described in the head and neck in advanced stages with reports of spread to the larynx, oral cavity, oropharynx, hypopharynx, cervical esophagus, paranasal sinuses, and the aerodigestive tract [3,8,15,16,22]. If peripheral blood involvement is present, patients are considered to have Sezary syndrome (SS) [29]. SS used to be considered an erythrodermic leukemic variant of MF but current classification systems categorize it as a separate entity [29].

Skin biopsy with histology is still regarded as the single most accurate diagnostic tool for MF diagnosis [5]. MF is classified according to the TNMB system, in which T, N, M, B represent skin (T), lymph nodes (N), visceral involvement (M), and blood (B). Additionally, the International Society for Cutaneous Lymphoma developed an algorithm for the diagnosis of early MF. It is a point system based upon

Figure 1: Skin changes of mycosis fungoides of the right cervical facial region.
clinical, histopathologic, molecular, and immunopathologic criteria [21]. Prognosis varies with the extent of skin involvement and stage, as well as presence of extracutaneous disease. One retrospective study of 122 patients with limited plaque disease (stage IA) showed a normal life expectancy when compared to a control population, controlled for age, sex, and race and mortality typically was not attributed to MF [12]. Generalized plaque disease without extracutaneous involvement (Stage IB and IIA) confers a median survival of approximately 11.7 years [11]. Cutaneous tumor (Stage IIB) or generalized erythroderma (Stage III) without extracutaneous involvement results in a bleaker prognosis with a median survival between 3.4 and 4.7 years. Patients with extracutaneous involvement (Stage IV) have the worst prognosis with a median survival of less than 4 years [1]. It should also be noted that other prognostic factors include age at disease presentation as well as peripheral blood involvement [29] which can affect predicted survival.

The cause of MF is unclear. Environmental and occupational exposure to chemicals and solvents have recently been implicated as one etiology; however, a large case-controlled study failed to support this hypothesis [28]. Other hypotheses include genetic and epigenetic etiologies [24, 27]. Currently, no consensus exists as to the definitive etiology of the disease.

Treatment options vary based on extent of skin involvement and disease stage. The standard treatment options for the earlier stages include topical therapeutic measures, such as mechlorethamine hydrochloride (HN2), phototherapy ultraviolet B (UVB), psoralen and ultraviolet A (PUVA), and localized electron beam radiotherapy (EBRT). These are used independently or in combination depending on the disease stage. More advanced disease may require systemic chemotherapy, sometimes with radiation or interferon-α [29].

Recent studies show an increased risk of second malignancies (primarily hematological malignancies) with MF [7, 8]. We present two patients, both with histories of diagnosed MF, who have subsequently developed secondary head and neck malignancies.

2. Patients and methods

Our first patient was a 57-year-old African American female initially presented with numbness to the right side of her tongue in October 2010. MRI showed a mass in the superior portion of the right submandibular gland, measuring 2.2 cm in dimension (Figure 2). Past medical history included gastroesophageal reflux disease, hypertension, intermittent dysphagia, asthma, arthritis as well as MF. Details about her MF (i.e., stage and treatment) were not available. She also had a family history of head and neck cancer in her paternal grandmother.

In late-March 2011, the patient underwent a mandibulectomy and resection of the tumor with a right neck dissection. Pathology showed a low grade mucoepidermoid carcinoma with some extension into the right floor of the mouth. The tumor measured $1.7 \times 1.5 \times 1.5$ cm with negative surgical margins and extensive perineural invasion. She was staged as T3N0M0 mucoepidermoid carcinoma of the right submandibular gland and completed a 6-week postoperative intensity modulated radiation therapy (60.2 Gy) in mid-July 2011. An MRI in February 2012 showed no evidence of recurrence or residual disease.

The second patient, a 31-year-old male of Pacific Island origin, first noticed skin lesions in 2001. He was not diagnosed with MF until 2006. Details about staging and treatment were unavailable. In April 2011, the patient presented with left cervical adenopathy, fever, and weight gain. Physical examination was unremarkable but a CT scan of the neck showed metastatic-appearing lymphadenopathy at levels 3, 4, and likely 6 along with a heterogeneous appearing thyroid mass. The patient underwent PET imaging that showed hypermetabolic activity associated with hypervascular left neck adenopathy as well as mild activity in a left inguinal lymph node (benign after biopsy). At the time of presentation, this patient had no difficulty swallowing or breathing and no prior history of thyroid cancer. He did have family history of thyroid cancer in his grandmother.

In May 2011, thyroid ultrasound showed mild generalized enlargement of both thyroid lobes with some cystic areas, a small calcification of the upper pole of the left lobe, as well as multiple vascular enlarged lymph nodes in the left supraclavicular region. Care was delayed due to patient family circumstances and his workup resumed in October 2011 due to a core needle biopsy that showed papillary thyroid

![Image](image_url)
carcinoma. A CT of the chest was performed in December 2011 that showed no evidence of metastatic disease. A neck CT was repeated and confirmed stable disease with moderately large volume of left mid to supraclavicular malignant adenopathy (Figures 3(a) and 3(b)). At this time, the patient was referred to Otolaryngology for evaluation and treatment. The patient underwent total thyroidectomy, central neck dissection, and left modified radical neck dissection in January 2012 for T3N1bM0 papillary thyroid carcinoma with right level VI metastases. In February 2012 he received I-131 (200 mCi) and there has been no evidence of disease since that time.

A PubMed search was performed to identify any articles whose focus was on second primary malignancies in the head and neck in patients with MF.

3. Results

We identified no published data that stressed a possible relationship between MF and head and neck second primary tumors. Second primary cancers have been reported in the pharynx \((n = 5)\), “nose, nasal cavity, and middle ear” \((n = 1)\), and sinuses \((n = 1)\) [8]. Additionally, mucosal squamous cell carcinoma (SCC) has been reported in the hard palate \((n = 1)\) [23], tongue \((n = 1)\) [23], and piriform sinus—with a history of radiation treatment \((n = 1)\) [19]. Cutaneous SCC has been reported on the forehead \((n = 1)\) [23] and ear \((n = 2)\) [23], although no differences in propensity for head and neck cancers was reported compared to other cutaneous locations. Cancers have also been described in the trachea [2,10] and bronchus [8] as well as the larynx \((n = 2)\) [8]. Kantor et al. described a three-fold increase in the number of laryngeal second primary tumors in patients with MF [10]. Finally, Huang et al. included a report of a germinoma of the thymus in their analysis of second malignant neoplasms in patients with MF as well as two “endocrine” tumors [8]. It is uncertain which endocrine organs were involved.

4. Discussion

Second primary tumors in MF are not uncommon and have a 2:1 male predominance [8]. Two studies have reported that approximately 5–6% of patients who develop MF will develop a second cancer [2,10]. Due to diagnostic difficulties and the indolent course of MF, the diagnosis is often delayed 4–10 years from the appearance of skin lesions [2,8,23]. Interestingly, Scarisbrick et al. reported that 16 out of 71 (23%) patients with SS developed second primary tumors. Of those with SS who develop second primary tumors, 31% involved the head and neck and 60% of those were cutaneous neoplasms [23].

The most common cause of a second neoplasm in MF is thought to be due to chronic immunosuppression from immune dysfunction [4,9,20]. Patients with MF have impaired cellular and humoral immunity. MF is an established risk factor for lymphoproliferative disease as well as cutaneous malignancies [4]. Pielop et al. observed that the carcinogenic or immunosuppressive effects of MF therapy cannot completely account for the development of melanoma [20]. Other authors have suggested that the altered immune responses in MF, particularly with more advanced stages, in addition to the effects of radiation therapy, alkylating agents, and PUVA therapy may make MF patients more prone to develop a second malignancy [10,18]. However, Pielop et al. observed that most patients...
who developed melanoma after the diagnosis of MF had early stage MF. As MF progresses to SS there is a change in the cytokine profile with concomitant change in T-cell function [13] and patients with erythrodermic MF often have markedly depressed levels of normal blood T-cells to the range seen in advanced AIDS [6]. These data support the hypothesis that immune dysfunction may predispose patients to a second neoplasm.

Another potential cause of increased second malignancies in MF patients is genetic. Pielop et al. observed that 61% of sampled MF lesions had p16 gene alterations, a tumor suppressor often involved in the development of melanoma [20]. While no other data currently exist with respect to possible genetic causes of second neoplasms, molecular causes may be responsible for the greater risk observed. Further research is needed to clarify this potential relationship.

Most second primary tumors associated with MF do not involve the head and neck. Some common malignancies reported involve the lung [10,26], colon [8,10], urinary system [8,19], and blood [8,10,26]. Additionally, cutaneous malignancies are well described in patients with a history of MF [8,14,25] with some thoughts that treatment modalities may confer increased risk [4,18,25]. One study reported greater than 100 fold increased risk of developing malignant melanoma [4], and another suggested a relative risk of 15.3 [20]. Data do not demonstrate a predilection for the head and neck, although reports of involvement of the ear, cheek, and nose are published [4,14].

Most of the cases of head and neck second primary malignancies were reported as having been diagnosed at least 2 months after the diagnosis of MF was made [2,8,10]. There are three reports of head and neck malignancies that were diagnosed shortly before the diagnosis of MF was made and include melanoma [4,20] and a case report of leiomyosarcoma of the larynx [9]. We mention them due to the common 4–10-year delay in diagnosis of MF [2] and suspect that at least some of these tumors may have developed after the onset of the skin rash associated with MF. However, we feel that only including cases that appeared two months after the diagnosis of MF was made is more reliable simply because most patients with a new cancer diagnosis will undergo a thorough workup by their oncologist which takes less than two months to complete.

Most of the reports of second neoplasms in MF give excellent overviews of the range of cancers seen in patients with MF, but do not describe the second primary tumor in detail. Specifically, little is said about the histology, staging, disease course, and patient risk factors for second primary tumors. This may be due to a lack of availability of these data. Nevertheless, we feel it is important to begin such a dialogue specific to head and neck second primary malignancies in patients with a history of MF.

5. Summary
MF may confer increased risk of the development of a second primary malignancy located in the head and neck. Otolaryngologists should be aware of the clinical presentation of MF and this potential association.

References


