Connective Tissue Disease Coincident With Nasopharyngeal Carcinoma

Two Sporadic Cases in a Western Population

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Objectives: To increase awareness of the potential coexistence of connective tissue disease and nasopharyngeal carcinoma in a Western population, to consider possible causes for this phenomenon, and to provide recommendations for clinical management.

Design: Case report.

Setting: Academic tertiary referral practice.

Patients: Ninety-four patients with nasopharyngeal carcinoma were initially treated, and 20 were followed for 10 years. Of these, 2 were diagnosed as having coexistent connective tissue disease.

Main Outcome Measure: The clinical course of coexisting diseases.

Results: Most previous reports of the coexistence of nasopharyngeal carcinoma and connective tissue disease involve southern Chinese populations. There are distinct similarities between those series and the cases presented herein. The association can take several forms with differing order of presentation and spectrum of symptoms. A variety of mechanisms have been proposed for the dual development of the 2 disease states.

Conclusions: Connective tissue disease and nasopharyngeal carcinoma may coexist in white patients in a manner similar to that seen in Asian populations. Awareness of this possibility is an indication for special screening measures.


Connective Tissue diseases (CTDs), including dermatomyositis (DM) and scleroderma (SD), have been reported to be associated with a variety of malignancies. In the upper aerodigestive tract, this phenomenon is seen most commonly with nasopharyngeal carcinoma (NPC), which is a rare disease among whites but is endemic among the southern Chinese. The first cases of NPC associated with CTD were reported in 1969. Since that time, a review of the literature shows that approximately 100 such cases have been reported (Table 1). One study cited a 0.086% incidence of DM in patients with NPC. This clinical entity has mainly been described in patients from southern Chinese groups, but it has received much less attention for patients in the West. Among North Americans of non-Asian descent, NPC is a rare disease. Similarly, CTDs are uncommon.

Dermatomyositis is a severe systemic disorder characterized by typical cutaneous lesions and an inflammatory myopathy. The 5 main diagnostic findings of DM include (1) systemic proximal muscle weakness, with or without dysphagia or respiratory muscle involvement; (2) abnormal muscle biopsy findings; (3) elevated skeletal muscle–derived enzymes; (4) abnormal electromyographic findings; and (5) a typical skin eruption (Gottron papules) overlying the knuckles, elbows, and knee joints. Special skin features include a characteristic heliotrope rash on exposed surfaces, periungual telangiectasia, and poikiloderma.

Scleroderma, or systemic sclerosis, is manifested by pathologic fibrosis of the skin and internal organs, including the lungs and kidneys. Patients may die of pulmonary fibrosis, pulmonary hypertension, or renal crisis. Ten-year survival for patients with SD is approximately 50%. In addition, there is a known association of SD with malignancy, particularly lung cancer. In most cases, the cancer is discovered years after the CTD diagnosis is made, although malignancy can precede the on-
set of skin disease. An “overlap syndrome” has been described consisting of features of DM and other CTDs, including SD or systemic lupus erythematosus. The presence of antinuclear antibodies in a patient with DM is indicative of this syndrome.

A common cause of CTD in the setting of NPC has been suggested by many researchers. The mechanism of the link between NPC and CTD is unknown. The coincidence of 2 unusual disease states in a recognized pattern raises questions that could provide leads for advances in the diagnosis and treatment of each. There are a variety of ways in which such a link could occur. One disease entity may contribute to the development of the other. Indeed, DM is known to occur rarely as a paraneoplastic syndrome associated with a variety of malignancies. Alternatively, the 2 entities may have a common genetic susceptibility, perhaps associated with a particular major histocompatibility genotype, or an association with Epstein-Barr virus (EBV) antigens.

The incidence of the paraneoplastic form of DM has been reported to range from 6.7% to 52.2% of all DM cases. However, in the West, where the incidence of NPC is very low, the effect of the coincident CTD and its impact on the clinical course of NPC remain unclear.

The Johns Hopkins Cancer Center tumor registry was searched for new cases of NPC diagnosed between January 1, 1990, and December 31, 2000; 94 patients were found. A departmental computerized tumor registry was also searched to identify 20 cases that were treated by members of the Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins Medical Center. This article presents the experience gained by treating 2 of these patients (both white) with NPC and intercurrent CTD. In one patient, the CTD appeared just before diagnosis of NPC, in the other, CTD was recognized several years later. In both patients, the manifestations of CTD combined with those of radiation therapy to produce severe dysphagia, sinusitis, otitis, and local skin problems. An awareness of the association of these diseases in the West is of particular importance to the otorhinolaryngology community, which is responsible for early cancer diagnosis and implementation of appropriate therapy. Our experience is consistent with the reported literature, which indicates that screening of the nasopharynx in patients older than 40 years with CTD is indicated to rule out associated NPC.

### Table 1. Reported Rates of Cancer, Nasopharyngeal Carcinoma (NPC), and Connective Tissue Disease (CTD)*

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>CTD</th>
<th>Cancer</th>
<th>NPC and CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al, 1996</td>
<td>China</td>
<td>70 899 NPC</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Peng et al, 1995</td>
<td>Taiwan</td>
<td>104 DM</td>
<td>27 All  types</td>
<td>17</td>
</tr>
<tr>
<td>Leow and Goh, 1997</td>
<td>Singapore</td>
<td>38 DM</td>
<td>12 All types</td>
<td>5</td>
</tr>
<tr>
<td>Teo et al, 1998</td>
<td>Hong Kong</td>
<td>1154 NPC</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Arirarb et al, 1995</td>
<td>Finland</td>
<td>175 PM/71 DM</td>
<td>34 All types</td>
<td>0</td>
</tr>
<tr>
<td>Present study</td>
<td>United States</td>
<td>20 NPC</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** DM, dermatomyositis; PM, polymyositis.

### REPORT OF CASES

**CASE 1**

A 39-year-old white man was seen at the Department of Otolaryngology–Head and Neck Surgery at The Johns Hopkins Medical Center for symptoms of sinusitis. He had been diagnosed a year earlier as having SD and myositis (overlap syndrome). The CTD was manifested by Raynaud phenomenon and generalized muscle weakness. His head and neck complaints consisted of a 2-month history of facial pain and pressure, with new-onset left-sided cranial nerve VI palsy, frontal headaches, nasal obstruction, and postnasal drip. A sphenoid mass was observed endoscopically; however, biopsy samples showed no evidence of vasculitis or malignancy. Three months later, a right-sided neck mass was noted, and fine-needle aspiration biopsy confirmed the presence of metastatic squamous cell carcinoma (SCC). At that time, a repeated biopsy of the nasopharynx documented the presence of a primary tumor, moderately differentiated SCC, extending from the fossa of Rosenmüller along the right lateral pharyngeal wall and into the soft palate. Computed tomographic scans documented parapharyngeal extension of the tumor and a second suspicious lymph node. Clinical staging according to the TNM staging system (American Joint Committee on Cancer) was thus T3 N2, stage IV.

Treatment was initiated consisting of cis-platinum and 5-fluorouracil concomitant with external beam radiation therapy to 6120 rad (61.2 Gy) followed by an interstitial boost with iridium 192 to 8000 rad (80.0 Gy). Eight months after the end of therapy, the patient was without evidence of malignant disease but had developed dysphagia. A video-esophagogram documented poor laryngeal elevation, absence of epiglottic tilt, poor pharyngeal contraction, nasopharyngeal reflux, and early cri-copharyngeal closure, with pooling of secretions and over-flow aspiration of thin liquids. At the same time, diffuse skin changes were noted, especially in the lower extremities. Corticosteroid treatment consisting of prednisone, 10 mg/d, was initiated. Severe restrictive lung disease was documented by pulmonary function studies. The CTD was managed medically, and the patient deteriorated gradually, developing severe kyphosis, diffuse edema and cushingoid features, dyspnea, copious nasal mucoid discharge, and otitis externa and media. Finally, 6 years af-
ter the end of treatment, a recurrence of NPC was documented on a biopsy sample from a new nasal mass, and the patient died of the combination of debilitating and malignant diseases.

CASE 2

A 33-year-old white woman had a right neck mass that was found to be poorly differentiated SCC by fine-needle aspiration. An ipsilateral primary tumor was discovered in the nasopharynx, and she underwent 7000 rad (70.0 Gy) of external beam radiation therapy for her T1 N1 NPC. She did reasonably well for 6 years before developing severe dysphagia with dehydration and pneumonia. A videoesophagogram showed pooling of secretions in the vallecula, poor pharyngeal stripping requiring frequent swallow- 

s of liquid to rinse solid boluses, and laryngeal penetration with thin liquids. The swallowing dysfunction was judged to be a severe manifestation of postirradiation xerostomia until the patient developed Raynaud phenomenon after another 6 years (a total of 12 years after irradiation). Serum test results demonstrated no autoantibodies; however, a diagnosis of overlap syndrome with clinical manifestations of DM and SD was made. The patient developed hoarseness and restrictive pulmonary disease, sclerodactyly, elevated creatinine kinase levels, atypical Gottron papules, a heliotropic rash, and “mechanic’s hand.” She was treated with prednisone, 40 mg/d, and is currently alive but severely debilitated.

WORLDWIDE INCIDENCE

First described in 1916 by Stertz,11 the association of CTD with malignancy has been reported sporadically in recent decades. Dermatomyositis seems to have a relatively robust association with malignancy, with studies showing a frequency of cancer in the DM population of 15% to 34% in some medical centers. Williams12 reviewed 590 cases of DM in an early meta-analysis of the literature and found 92 individuals with malignancy; none of these cases were NPC. Barnes13 reviewed 15 cases of NPC in 258 patients with DM, two thirds of which were from Asia. In the East, this association seems particularly strong (Table 1). Although in the Orient NPC is more frequently found in the general population and in patients with DM, the proportion with NPC and DM is approximately 3 to 4 times more prevalent than in the general population.1 In Hong Kong, 10 of 1154 patients with NPC developed DM.3 Three of these individuals experienced severe complications of irradiation, including cranial nerve palsy (delayed), chronic skin ulceration, and fistula formation. Hu et al2 reviewed 61 cases of NPC with DM from more than 70000 cases of NPC in 25 years. Their analysis led to an estimated prevalence of this disease combination of 0.086% of all patients with NPC seen and 0.027% of all malignant tumors. A recent study3 from Taiwan described 17 cases of NPC in patients with DM. Conversely, in this study, 27 of 104 patients with DM had an associated malignancy. In 11 cases, the cancer arose in a site other than the nasopharynx (2 in the lung, 2 on the skin, 2 in the bladder, 2 hepatocellular, 2 tonsillar, and 1 unknown primary metastatic to the abdomen). All patients had typical skin manifestations of DM, and most had myositis. In contrast to the study7 from Hong Kong, radiation therapy for the NPC resulted in no severe, immediate skin complications.

In white patients, a variety of malignancies are associated with DM, but NPC is not found in published studies. In a review of the literature encompassing 590 Western patients with DM, 92 (16%) had associated malignancy. Cancers of the lung and stomach were most frequent among men in this group, whereas women were most likely to have breast or ovarian cancer.12 Similarly, of 71 Finnish patients with DM, 19 had cancer, including 7 with malignancy of the gastrointestinal tract, 3 of the lung, 1 of the breast, and 4 of the ovary.6

POSSIBLE MECHANISTIC LINKS BETWEEN NPC AND CTD

There are several ways in which mechanistic factors may link CTD with NPC. Broad categories of possible mechanisms of linkage are listed in Table 2. Patterns of the timing of the onset of the diseases, coexistence of CTD with other malignancies, and other observations may provide insight as to the most likely explanation for the juxtaposition of these rare diseases. However, the occasionally indolent, gradual onset of NPC and CTD makes it difficult to use timing of diagnosis as an indicator of sequence of events and hence causation.

As listed in Table 2, CTD in the setting of NPC may result from immune disregulation, leading to aberrant recognition of normal tissues after viral-mediated transformation and tumor formation. Connective tissue diseases are thought to be autoimmune disorders in which antibodies directed against normal antigens are aberrantly produced by the immune system and mediate clinical manifestations of disease. Cancer occurs when a series of genetic alterations accumulate in a transformed cell, conferring a malignant phenotype, including alterations in cellular behavior and in protein expression. It follows that one potential pathway for a linkage between CTD and NPC may be the production of a tumor-related antigen that induces an autoimmune response be-

Table 2. Possible Mechanisms of Association of Connective Tissue Disease (CTD) and Nasopharyngeal Carcinoma

<table>
<thead>
<tr>
<th>POSSIBLE MECHANISTIC LINKS</th>
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<tbody>
<tr>
<td>Cancer causes or predisposes to CTD</td>
</tr>
<tr>
<td>- Tumor-associated antigen (including viral antigen) induces cross-reactive autoimmune response (“molecular mimicry”)</td>
</tr>
<tr>
<td>- Paraneoplastic phenomenon induces CTD (e, secretion of biologically active molecule)</td>
</tr>
<tr>
<td>CTD predisposes to cancer</td>
</tr>
<tr>
<td>- Autoimmune-mediated tissue damage permits Epstein-Barr virus transformation</td>
</tr>
<tr>
<td>- Immune dysregulation enables tumorigenesis (or other immunodeficiency-mediated tumorigenesis)</td>
</tr>
<tr>
<td>Cancer treatment causes CTD</td>
</tr>
<tr>
<td>- Irradiation or chemotherapy effects unmask autoimmune antigen</td>
</tr>
<tr>
<td>Common genetic predisposition</td>
</tr>
<tr>
<td>- Human leukocyte antigen linkage, immune response polymorphism</td>
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</tbody>
</table>
cause of the homologous sequence with some normal antigen (“molecular mimicry”).

Epstein-Barr virus is widely accepted as an etiologic agent in NPC tumorigenesis. Activation of an immune response to a “cryptic” epitope not produced or exposed before viral infection may result from the matching of a viral epitope to a mutated, or endogenous, antigen. For example, an EBV protein, BOLF1, has epitopes shared with the hypervariable region of HLA that is associated with the pauciarticular form of juvenile arthritis, suggesting a link to other collagen diseases, including SD.14 Several nuclear antigens are remarkable in displaying homologous sequences with immunosuppressive viruses. There are 4 homologous sequences between the systemic lupus erythematosus–associated 70-kd antigen and EBV.15 These homologous sequences cluster within regions known to contain epitopes for human autoantibodies.

The unmasking of cryptic immune epitopes in the setting of EBV infection may enable the activation and expansion of autoreactive immune response, perhaps through the dysfunction of suppressor T cells, leading to clinical connective tissue manifestations (antibody-antigen complex deposition, complement fixation, and tissue damage). An immunologic phenomenon termed “epitope spreading” has been increasingly recognized as an important pathogenic mechanism responsible for the initiation or progression of autoimmune diseases.16 This reflects a positive feedback cascade, with additional self-antigenic targets attacked through the initial response to the viral antigen. The potential clinical significance is apparent in the hypothetical setting of therapeutic transfer of NPC antigen-specific T cells (adoptive transfer) for tumor immunotherapy. If a patient with NPC also has an autoimmune CTD, such immune cell transfer might be expected to have deleterious consequences.

The Ku protein, which functions in the repair of DNA double-strand breaks, is a major target of autoantibodies in a subset of Japanese patients with SD-polymyositis overlap syndrome. In addition to Ku, 3 other proteins in the DNA repair pathway have been identified as autoantigens: XRCC4, DNA ligase 4, and the DNA-dependent protein kinase catalytic subunit. It has been hypothesized that DNA damage induces formation of nucleoprotein complexes with the formation of novel conformational epitopes.17 Consistent with this evidence, cellular apoptosis increasingly has been linked to autoimmune flares, particularly after UV irradiation. Thus, the DNA damage and apoptosis secondary to tumorigenesis or irradiation and chemotherapy may induce autoimmunity, resulting in the overlap syndrome. Other antigens implicated in SD include DNA topoisomerase 118 and various centromere proteins,19 whereas autoantibodies for DM may be directed against epitopes on the HLA-DR B chain.20 Although certain HLA alleles have been implicated in the predilection to develop NPC or CTDs, we are not aware of any common major histocompatibility complex molecules that are overrepresented in the few patients reported to manifest both diseases. Whether this is owing to an actual lack of an associated HLA-mediated immune response or to the infrequency of these patients in a single medical center remains to be established.

Stone21 proposed multiple trigger mechanisms caused by malignancy to account for the onset of DM. He cites the changes in extracellular membrane around tumors with entry into the circulation of altered glycosaminoglycans.22 The secretion of biologically active molecules by the transformed NPC cells may be another factor, resulting in a paraneoplastic phenomenon inducing CTD. Both SCC and SD involve aberrations of the transforming growth factor (TGF) signaling pathway. Expression of TGF-β decreases in poorly differentiated SCC, and Smad2 expression may be lost.22 In SD, basal level and TGF-β–inducible Smad7 expression are selectively decreased and Smad3 expression is increased; TGF-α signaling events are increased in SD fibroblasts. These alterations may cause TGF-β hyperresponsiveness in SD.23 Tumor-induced changes in TGF, epidermal growth factor receptor, and epidermal growth factor ligand expression may recreate similar alterations in the TGF–epidermal growth factor pathway, producing CTD.

The use of cytotoxic therapy for DM is not thought to increase the risk of malignancy. In fact, the cancer risk was higher in patients not receiving cytotoxic drugs. On the other hand, the possible induction of CTD due to therapeutic modalities is occasionally raised in the literature. Connective tissue disease has been reported after exposure to chemicals and drugs, including chemotherapeutic agents. According to Airio et al,24 after radiation therapy, exacerbation or de novo occurrence of systemic sclerosis has been reported occasionally. This reaction must be distinguished from the typical fibrosis commonly seen after head and neck therapeutic irradiation in our patients. Scleroderma has been reported to follow radiotherapy in rare cases. The fibrosis commonly seen after radiation therapy, however, is limited in extent and does not progress. In one study,24 3 patients treated with radiation for breast cancer and NPC developed SD within a month of treatment. Another recent single case report was published describing a patient who developed rapidly progressing SD 10 months after diagnosis of NPC. He underwent surgery, cisplatinum and 5-fluorouracil chemotherapy, followed by radiation therapy. Seven months after therapy he developed skin tightness, Raynaud phenomenon, hoarseness, and dysphagia.25 This case is reminiscent of our case 2, although in our patient the delay before the development of CTD was much longer.

OBSERVATIONS FROM THE JOHNS HOPKINS PATIENT EXPERIENCE

The 2 patients followed at The Johns Hopkins Medical Center demonstrate several features of the association between NPC and CTD reported in the endemic Eastern series. In particular, the timing of the onset of disease varied. Most patients described in the literature developed CTD before the diagnosis of cancer, as in case 1; however, some others developed CTD after treatment for NPC, as in case 2. The length of the interval between treatment for NPC and the onset of CTD symptoms in case 2 is unique in the literature. Indeed, the initial clinical impression when that patient developed dysphagia was of delayed onset of radiation-induced deglution compromise. Only when the dysphagia became severe and other...
skin manifestations of CTD appeared was the actual diagnosis made. On the other hand, in retrospect it would seem that NPC and CTD arose nearly simultaneously in case 1, although the documentation of NPC was delayed for more than a year owing to the inaccessibility of the cancer.

In both cases, the CTD was manifested as an overlap of symptoms not classic for DM or SD. Symptoms of ear, sinus, and pharyngeal dysfunction are typical after radiation therapy applied to the Waldeyer ring, but both patients also displayed Raynaud phenomenon, diffuse skin thickening, rashes, and restrictive lung disease. Other features, such as facial swelling, were likely the result of prednisone therapy.

Both of our patients had smoked in the past. Histologic features of the tumor were poorly differentiated in case 2 and moderately differentiated in case 1. Testing for EBV was not performed in either patient, and standard autoantibody titers for CTD (antinuclear antibodies and anti–Jo-1) were negative in both cases. Both patients were relatively young white adults, an unusual demographic setting for NPC and for NPC-associated CTD. In most such cases in the literature, the afflicted patients were older than 40 years. However, a similar case has been reported in a 37-year-old Israeli with NPC and DM.

Three Tunisian patients aged 24, 40, and 65 years have also been described as having the same combination of diseases.

In the series by Hu et al and in the Tunisian patients, the clinical features of DM improved when the NPC was treated, suggesting a paraneoplastic cause for the CTD. This did not occur in our 2 cases, both of whom developed CTD in whom it worsened while the NPC was in remission.

CLINICAL IMPLICATIONS

Awareness that NPC and CTD may coexist could be useful in the treatment of patients under several circumstances. It has been suggested in the literature by several researchers that all patients with DM be screened for the possible presence of NPC. When NPC is diagnosed first, patients may be watched carefully for inordinately severe posttreatment dysphagia, dermal fibrosis, and other manifestations of CTD. Early intervention with corticosteroids and newer medications may benefit these individuals.

In the large study of 1154 patients with NPC from Hong Kong, 5- and 10-year survival rates were better in those with both diseases than in NPC controls without DM (age, sex, and stage matched). An unfavorable prognosis is thus not suggested when DM is associated with NPC.

CONCLUSIONS

This fascinating interaction between an unusual malignancy and CTD has been recognized for a century. It has profound implications for afflicted patients, rendering their quality of life and possibly their longevity much reduced. A variety of potential etiologic explanations have been suggested in the literature and must be carefully explored. In-deed, unraveling this mystery may yield clues to the pathogenesis of both diseases. Awareness of the potential association will enable health care providers, including head and neck surgeons, to better anticipate and diagnose disease and prescribe therapy aimed to reduce morbidity.

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REFERENCES