Cell-mediated immunity in nasopharyngeal carcinoma and allergic rhinitis: A controlled study

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Abstract
We conducted a prospective study of 60 patients in a tertiary care referral center to ascertain the status of cell-mediated immunity as determined by delayed hypersensitivity reactions in patients with nasopharyngeal carcinoma (NPC) or allergic rhinitis. Delayed hypersensitivity as detected by Mantoux testing is generally accepted as a reflection of the level of cell-mediated immunoactivity—the less hypersensitivity reaction that occurs, the lower the level of immunoactivity is, and vice versa. Our study population was made up of three groups: 20 newly diagnosed patients with NPC (pretreatment), 20 age- and sex-matched patients with allergic rhinitis, and 20 matched controls without either disease. A negative Mantoux test (0- to 5-mm induration) was seen in 13 patients with NPC (65.0%), in 17 patients with allergic rhinitis (85.0%), and in 16 controls (80.0%); none of these differences was statistically significant. However, it is interesting that while the NPC group had the lowest percentage of negative Mantoux results overall, it had the highest percentage of patients who had no reaction at all (i.e., 0-mm induration); a complete absence of any reaction was seen in 7 of the 13 Mantoux-negative NPC patients (53.8%), compared with 2 of the 17 Mantoux-negative allergic rhinitis patients (11.8%) and 3 of the 16 Mantoux-negative controls (18.8%). An absence of a reaction generally indicates a very limited degree of cell-mediated immunoactivity. Therefore, we conclude that patients with NPC appear to have significantly less cell-mediated immunity than do patients with allergic rhinitis and normal controls; no statistically significant difference was noted between the latter two groups.

Introduction
Nasopharyngeal carcinoma (NPC) is a common malignancy among adults seen at the University Malaya Medical Center in Kuala Lumpur. It carries a poor prognosis if it is not detected early.

The role of immunology in the treatment of oncologic disease is well established. Cytotoxic T cells and natural killer T cells are part of the highly efficient defense mechanism that keeps ectopic malignant cells in check. However, the factors that regulate this mechanism are still largely unclear.

Some recent studies have suggested the possibility that patients with NPC experience a reduction in cell-mediated immunoactivity. Moreover, NPC appears to have an inverse relationship with allergic rhinitis, and possible immunologic associations have been implied. The possibility of cross-reactivity between a type 1 hypersensitivity reaction (e.g., nasal allergy) and a type 4 hypersensitivity reaction (essentially cell-mediated immunoactivity) has been postulated. If this hypothesis is true, the degree of cell-mediated immunity should be lower in patients with NPC than in patients with allergic rhinitis. T-lymphocyte dysregulation has also been shown to play a major role in airway allergy.

The goal of this study was to ascertain the cell-mediated immune status of patients with NPC and to compare it with the status of patients with allergic rhinitis and normal controls.

Patients and methods
Candidates for this prospective study were recruited from the ENT clinic at our tertiary care referral center during 2003. Because a delayed hypersensitivity reaction to a previously sensitized antigen occurs, patients who had not been previously vaccinated with bacille Calmette-Guérin (BCG) were not eligible for this study. A negative BCG status was determined by a thorough history and by the absence of a BCG scar on the upper forearm. Also excluded were patients who were suspected of being immunocompromised and patients who had a history of pulmonary...
tuberculosis or who had been in close contact with such a patient. We chose 60 patients—36 men and 24 women—to serve as our study population. Based on their pathology, patients were assigned to one of three age- and sex-matched groups; each group was made up of 12 men and 8 women, aged 32 to 63 years (mean: 41):

- One group was made up of patients with newly diagnosed and as-yet-un-treated NPC. The presence of the cancer was confirmed by analysis of histologic specimens obtained from the postnasal space or the fossa of Rosenmüller.
- The second group was made up of patients who had a clinical diagnosis of allergic rhinitis.
- The control group was made up of subjects who had no history of allergic rhinitis or any malignancy.

After providing informed consent, all patients underwent a Mantoux test. Mantoux testing elicits a delayed hypersensitivity reaction to a previously sensitized antigen (a T-lymphocyte function), and it is generally accepted as a valid in vivo indicator of a patient’s level of cell-mediated immunity. A complete absence of a response generally indicates an impairment of T-cell function, which reflects a low degree of cell-mediated immunoactivity. Mantoux testing was performed with tuberculin purified protein derivative (PPD) RT 23 SSI (Statens Serum Institut; Copenhagen). Each vial contained 1 ml of tuberculin PPD at a strength of 2 TU/0.1 ml.

The results of all Mantoux tests were read approximately 72 hours after inoculation (most positive results become evident in 8 to 72 hours). Indurations were measured transversely to the long axis of the forearm with a clear, flexible scale. Results were categorized as negative (0- to 5-mm induration), positive (6 to 14 mm), and strongly positive (≥15 mm).

Results
A negative Mantoux test was seen in 13 patients with NPC (65.0%), in 17 patients with allergic rhinitis (85.0%), and in 16 controls (80.0%) (table). None of these differences was statistically significant.

The Mantoux results were statistically significant. The differences between the NPC group and both of the other two groups were statistically significant; the difference between the allergic rhinitis patients and the controls was not significant.

Discussion
NPC is one of the most common malignant tumors of the head and neck. It has a tendency to spread rapidly to the regional neck nodes and to metastasize to the bones, liver, and lungs. Its etiology is multifactorial; genetic factors, Epstein-Barr virus (EBV), and environmental factors that activate EBV have all been reported to contribute. Evidence is increasing that EBV plays the primary role in the development of NPC.

A delayed hypersensitivity test is an immune function assessment that measures the presence of activated T cells that recognize a certain substance. After an initial exposure to a foreign substance or antigen, the immune system creates antibodies and sensitized T cells. Both of these immune system agents respond when the body is re-exposed to the antigen. The antibodies, which are circulating proteins, respond within minutes and elicit an immediate hypersensitivity reaction. The T cells respond over a period of several days, and thus they elicit a delayed hypersensitivity reaction.

The reaction to tuberculin antigens, which is elicited by the Mantoux test, is a classic example of a delayed hypersensitivity reaction. The tuberculin skin test is able to assess the vitality of the T-cell response. The cascade of events initiated by T cells can lead to hardening (induration) and erythema at the injection site. An absence of reaction indicates a lack of T-cell responsiveness, which is a characteristic finding in patients with immune deficiency diseases. An intact immune system is essential for the development of a positive skin test; conversely, any impairment of the cell-mediated immune response generally results in a minimal or absent reaction and thus a negative test.

A delayed hypersensitivity test is performed for one of three reasons:

- to test for exposure to specific diseases, such as tuberculosis (Mantoux test)

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<th>Table. Results of Mantoux testing</th>
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<tr>
<td>Mantoux result (induration)</td>
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<tr>
<td>Positive (≥6 mm)</td>
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<td>6 to 14 mm</td>
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<td>≥15 mm (strongly positive)</td>
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• to test for allergic sensitivity to potential skin irritants (skin-prick test)
• to assess the vitality of the T-cell response as part of an evaluation of the immune system in patients with an infection, cancer, or an immune disorder, and as a screening tool for older patients, malnourished patients, and those who are scheduled to undergo organ transplantation.

Cell-mediated immunity is apparently an important element of the host defenses against cancer. A growing body of information on cell-mediated immunity to EBV is providing a strong basis for research on immunoreactivity in NPC. Cell-mediated immune responses to viruses and tumor-associated antigens may have implications for enhancing our knowledge of the etiology, diagnosis, and treatment of NPC in the near future.

Our finding that patients with NPC have a low degree of cell-mediated immunity confirms a finding by Hsu et al, who published the results of their study of 344 patients with NPC in 1980. Two years earlier, Chan et al reported that newly diagnosed NPC patients had an impaired T-cell function that was associated with poor survival.

The prognosis for patients with NPC is generally poor, largely because it is difficult to detect in its early stages. This cancer can arise secondary to the failure of an immunosurveillance mechanism in which immunoresponsive ness is extremely depressed. Immunologic status has been examined, and the clinical evaluation of immunotherap y and lymphocyte transfer has been performed by Tsukuda and Sawaki. They found that deficiencies of cellular immunity could be recognized through the various immunologic parameters and immunotherapy. They suggested that this is indispensable in this cancer treatment.

References