Patients with Fanconi anemia (FA) are at increased risk for head and neck cancer compared with the general population. Using FA as a model to study the natural history of head and neck cancer, David I. Kutler, MD, and colleagues have made exciting discoveries about the underlying mechanisms of carcinogenesis, which may ultimately help produce more effective and safer treatments for patients with FA.

The increased risk for cancer among patients with FA is thought to be attributable to instability of the genome, as evidenced by cellular hypersensitivity to DNA crosslinking agents and failure of chromosomal repair mechanisms. “The response to the severe DNA damage caused by diepoxybutane and mitomycin, for instance, is impaired in FA, and cells fail to correct the excessive chromosomal breakage and DNA crosslinking that occur when exposed to these agents,” said Dr. Kutler. The loss of genomic integrity is believed to contribute to the elevated risk for cancer in these patients.

Currently, Dr. Kutler is studying the cellular pathways of head and neck cancer in patients with FA at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. He was first drawn to studying FA after collaborating with Arleen Auerbach, PhD, a researcher at the Laboratory of Human Genetics and Hematology at Rockefeller University, and Bhuvanesh Singh, MD, PhD, from Memorial Sloan-Kettering Cancer Center, both in New York City. Dr. Auerbach had established the International Fanconi Anemia Registry (IFAR) to track patients with this rare disease. “She had observed through the registry that a relatively large number of FA patients developed head and neck cancers at a young age—20 to 30 years old—despite an absence of traditional risk factors for this malignancy, such as cigarette smoking or excessive use of alcohol,” said Dr. Kutler.

Dr. Auerbach asked Dr. Kutler to help her explore a possible relationship between the genetics of FA and the etiology of head and neck cancer. “Using FA as a model to study the natural history of head and neck cancer was a unique opportunity,” said Dr. Kutler, “because there are no other known head and neck cancer-predisposing syndromes that might offer insights into the pathogenetic etiology of this disease.”

Patients with FA are at especially increased risk for leukemias and squamous cell carcinomas (SCCs), usually in the upper aerodigestive, gastrointestinal, and anogenital tracts. FA is an autosomal recessive genetic disorder characterized by progressive bone marrow failure, various phenotypic malformations, and a predisposition to development of leukemia and lymphoma.

Sublingual Immunotherapy Gains Popularity

For the 40 to 50 million Americans who suffer from allergic diseases, there may be good news as the use of sublingual immunotherapy (SLIT) becomes more widespread. According to William Reisacher, MD, this technique “has been widely used in Europe since the 1980s, with a high success rate, but is now beginning to gain traction in the United States.”

Dr. Reisacher and colleagues in the Department of Otorhinolaryngology at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are prescribing SLIT for the oral delivery of safe and effective allergen-specific immunotherapy, traditionally given by subcutaneous (SC) injection. Hector Rodriguez, MD, and colleagues at NewYork-Presbyterian/ Columbia University Medical Center are exploring the use of SLIT as well.
Multidisciplinary Clinic Treats Pediatric Airway Disorders

The multidisciplinary pediatric airway clinic is a relatively new concept in medicine. A paradigm based on the diverse challenges associated with congenital or acquired airway problems in children, the clinics at NewYork-Presbyterian Hospital/Columbia University Medical Center and Weill Cornell Medical Center are staffed by a variety of upper airway specialists, all with special skill in working within the smaller spaces of the pediatric airway.

According to Robert Ward, MD, children with serious acquired or congenital airway defects are best managed in a specialized setting that caters to the pediatric patient. “With a multidisciplinary staff,” he advised, “the clinic offers the expertise of a variety of pediatric specialties, from general pediatrics, otolaryngology, and pulmonology to pediatric gastroenterologists, neurosurgeons, and/or speech therapists when needed, thus addressing all of the problems of pediatric airway disorders at a single location and in a coordinated fashion.”

Eli Grunstein, MD, added: “Congenital conditions such as laryngeal cleft or laryngomalacia may not be life-threatening but can cause difficulty swallowing and speech and voice dysfunctions that demand the skills of pediatricians, surgeons, and speech specialists at the same time.” Similarly, patients with airway scarring, with or without a tracheotomy tube in place, often require attention from a myriad of specialists. Furthermore, Dr. Grunstein noted, more serious problems can arise when children are born with tumors such as airway hemangiomas, which are typically benign but, based on location, may be life-threatening if they interfere with the patient’s airway.

The right vocal fold of a 39-year-old female patient is paralyzed and hypotonic, causing the patient to aspirate liquids and have a profoundly hoarse voice.

Figure 1. The right vocal fold of a 39-year-old female patient is paralyzed and hypotonic, causing the patient to aspirate liquids and have a profoundly hoarse voice.

Figure 2. One week after an injection of calcium hydroxylapatite paste to the right vocal fold, the vocal fold remains paralyzed but has good closure and both aspiration and hoarseness have resolved.
The multidisciplinary pediatric airway clinic at NewYork-Presbyterian/Columbia is “imminent,” said Dr. Grunstein, “with concept approval from the Departments of Pediatrics, Pediatric Pulmonology, and Pediatric Otolaryngology, and architecture assigned specifically for the purpose of pediatric outpatient and operative ENT care.” There are operating rooms designated for the pediatric clinic cases, an endoscopy suite with new equipment for pediatric upper aerodigestive tract endoscopy, and staffing by full-time pediatric anesthesiologists. It is hoped that the clinic will be ready and opened within the year.

Dr. Ward hopes to continue to build the concept of the specialty airway clinic and provide a learning opportunity that will benefit ENT specialists. “As we move into our new facility and the uptown clinic nears completion, our ongoing camaraderie, discussion, and cross-pollination of ideas should continue to further the growth of the pediatric airway clinic model.”

Contributing faculty for this article: Eli Grunstein, MD, and Robert F. Ward, MD

ability to breathe adequately (Figure). “In the clinic we tend to see the most severe cases, often referred from the intensive care unit or community otolaryngologists.”

Craniofacial anomalies are another frequent presentation at the pediatric airway clinic. “Infants born with small mandibles,” Dr. Ward said, “often have severe breathing problems, and children with cleft palates may need to see ENT surgeons as well as the plastic surgeon, dentist, and/or orthodontist.” In addition, acquired airway disorders, or iatrogenic problems such as vocal cord paralysis or tracheal stenosis related to frequent or long-term intubation, are a particular interest of Dr. Ward’s.

The airway clinic at NewYork-Presbyterian Hospital/Weill Cornell evolved over time, said Dr. Ward, “as a place where the necessary specialists can concentrate resources and provide comprehensive office care.” The success of the program is evident in the expansion of the clinic and its move to a new 4,000-square-foot space on East 72nd Street, complete with dedicated offices, nursing staff, equipment and toys, all in a child-centered setting.

Figure. a. Image depicts pediatric patient with a subglottic hemangioma. b. Laryngoscopy of a 1-year-old female patient with a history of prematurity, chronic lung disease, and prolonged intubation at birth reveals severe laryngeal stenosis. In preparation for laryngotracheal reconstruction, she was seen by pediatric pulmonologists and pediatric gastroenterologists. She underwent ph probe placement and upper endoscopy with biopsies. After confirming stable lung function and controlled reflux, she was scheduled for laryngotracheal reconstruction using a rib cartilage graft.

continued from SLIT, page 1

“After attempts at avoidance therapy and pharmacotherapy with antihistamines, decongestants, and nasal steroid sprays, people who do not achieve adequate symptom relief are good candidates for immunotherapy, and SLIT represents a promising advance over the SC injection approach,” advised Dr. Rodriguez.

Most of the literature to date on SLIT is based on European research, although large U.S. trials are under way, including a Weill Cornell Medical College study. “With about a 30% dropout with SC administration,” Dr. Reisacher said, “our first study is examining whether the dropout rate is improved among SLIT-treated patients.” A second trial, assessing whether preseason preventative therapy with SLIT can reduce symptoms of seasonal allergies, is being considered. “Patients with seasonal allergies to only 1 or 2 allergens generally are not offered SC immunotherapy, but this is a population who might benefit from the convenient and safe SLIT method,” emphasized Dr. Reisacher.

SLIT provokes the immune system with increasing amounts of allergen stimulus, thereby increasing tolerance to the antigen and reducing symptoms of seasonal or perennial inhalant allergies. Although it uses the same allergen extract and works by a mechanism similar to SC immunotherapy, the oral method is considered more convenient and safe. SLIT is administered via 3 daily drops of allergen extract solution under the tongue; the antigen is held for 1 to 2 minutes and then swallowed or spit out.

“Pharmacokinetic studies show that while the allergen remains in the oral mucosa for up to 40 hours, there is no evidence of systemic distribution,” said Dr. Reisacher, making this approach what he called a “full-body surveillance system,” wherein the immune system reacts systemically to a local stimulus (Clin Exp Allergy 2001;31[1]:54-60). The simplicity and safety of the oral administration, Dr. Rodriguez said, “allows for home-based self-medication, although the first dose is given in the doctor’s office.” It may also be a preferred option for children, particularly those with needle phobia.

In contrast, SC immunotherapy requires weekly office visits for injection of allergen, with dosage increases to achieve maximum efficacy. “Each visit for SC therapy includes a 20-minute wait after the injection, to be certain the patient does not have an anaphylactic reaction,” Dr. Reisacher said. Once a

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Photos courtesy of Eli Grunstein, MD.

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