

The role of chromosomal translocation (15;19) in the carcinoma of the upper aerodigestive tract in children

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OBJECTIVE: To further evaluate the role of chromosomal translocation (15;19) in the presentation of the carcinoma (CA) of the upper aerodigestive tract.

STUDY DESIGN AND SETTING: A retrospective study at a tertiary care pediatric medical center.

RESULTS: Seven patients with a mean age of 12 years presented with CA of nasopharynx (N = 2), sinonasal region (N = 1), parotid gland (N = 2), or larynx (N = 2). Treatments included combinations of surgery (N = 5), chemotherapy (N = 5), and radiation therapy (N = 4). One patient with sinonasal CA and one patient with laryngeal CA had chromosomal translocation (15;19); these patients both died of their disease with a mean survival of 6 months. The 5 patients without translocation (15;19) responded well to treatment and are disease-free with a mean follow-up of 47 months.

CONCLUSION: The preliminary results appear to indicate poor prognosis associated with the presentation of chromosomal translocation (15;19) despite aggressive multi-modality treatment. Further investigation is needed to better understand the cause and relationship of the translocation (15;19) and

aggressive behavior of these tumors. (Otolaryngol Head Neck Surg 2003;129:698-704.)

Carcinoma (CA) of aerodigestive tract is rare in children and young adults. Although the behavior of the disease is similar in children and adults, there are differences in the patterns of occurrence, role of predisposing factors, and considerations for treatment. In the past 2 decades, there has been a surge of interest in investigating genetic mechanisms underlying the growth of various neoplasms. In solid tumors, the role of acquired chromosomal translocations has been well investigated only in sarcoma. Examples of well-characterized translocations include those of synovial sarcoma (X;18), Ewing's sarcoma (11;12), and alveolar rhabdomyosarcoma (2;13). Assays for characteristic translocations in these tumors are now used for diagnostic and prognostic purposes. Investigation of such chromosomal aberrations has led in many cases to discoveries about the molecular mechanisms of tumorigenesis, and this has led to exciting possibilities for novel disease-specific therapies.

Characteristic recurrent chromosomal translocations were not recognized in carcinomas, with the exception of thyroid¹ and papillary renal cell carcinoma,² until recent descriptions of t(15;19) in aggressive CA of the upper aerodigestive tract. The chromosomal translocation (15;19) has been reported as a cytogenetic hallmark of an aggressive form of CA in 6 children and young adults.³⁻⁷ All 6 patients presented with CA in the areas of head, neck, or chest and died quickly of their disease despite aggressive treatment. Two patients from our institution with translocation (15;19) have been reported earlier^{7,8} and are included in this article for further review. We reviewed our institutional experience with CA of upper aerodigestive tract to further evaluate the role of chromosomal translocation (15;19) in the presentation and management of these patients.

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Table 1. Carcinoma of the aerodigestive tract

Patient	Sex	Age Years	Initial Presentation	Location	Pathology	Stage	PMH	Treat- ment	Survival Months	Translo- cation 15;19	Status
1	F	12	Nasal obstruction	Nasopharynx	Carcinoma, poorly differentiated	T4N0M0	None	C, R	3	Yes	DOD
2	M	16	Nasal obstruction, epistaxis	Sinonasal	SCCA, poorly differentiated	T3N0M0	None	C, S	11	No	NED
3	F	15	Nasal obstruction	Nasopharynx	Carcinoma, poorly differentiated	T2bN0M0	None	S, C, R	116	No	NED
4	F	3	Parotid mass	Parotid gland	Mucoepidermoid CA, low grade	T1N0M0	None	S	34	No	NED
5	M	12	Parotid mass	Parotid gland	Mucoepidermoid CA, low grade	T1N0M0	None	S	69	No	NED
6	F	13	Sore throat	Larynx	SCCA, poorly differentiated	T2N2bM0	None	C, R, S	9	Yes	DOD
7	F	14	Hoarseness	Larynx	SCCA, well-differentiated	T3N0M0	None	C, R	4	No	NED

CA, Carcinoma.
C, Chemotherapy.
R, Radiation therapy.
S, Surgery.
DOD, Dead of disease.
NED, No evidence of disease.
SCCA, Squamous cell carcinoma.

MATERIAL AND METHODS

Seven patients were identified with CA of upper aerodigestive tract between 1993 and 2000 at the Children's Hospital in Boston. All data with respect to age, sex, initial presentation, pathologic and cytogenetic features, and treatment were reviewed. Pathologic features were characterized based on review of all surgical pathology and autopsy material. Fluorescence in situ hybridization for t(15; 19) was performed as previously described.⁸

RESULTS

Seven patients with age range of 3 to 16 years (mean, 12 years) presented with CA in different areas of the upper aerodigestive tract. There were 2 men and 5 women. Initial presentation included nasal obstruction, parotid mass, sore throat, or hoarseness (Table 1). There was no significant medical or family history, and no exposure to tobacco or alcohol, in any of the patients. The location of CA included: nasopharynx (N = 2), sinonasal region (N = 1), parotid gland (N = 2), larynx (N = 2) (Fig 1). Histologic subtypes included poorly differentiated squamous cell carcinoma (SCCA) (N = 2); low grade mucoepider-

moid CA (N = 2); well-differentiated SCCA (N = 1); and poorly differentiated CA (N = 2) (Table 1).

All patients were evaluated in the departments of otolaryngology and radiation and medical oncology and presented at the head and neck tumor conference. Treatment options were based on the current protocols at the Center for Head and Neck and Skull Base Surgery at the Children's Hospital, Boston, and the Dana-Farber Cancer Institute. Treatments included combinations of surgery (N = 5), chemotherapy (N = 5), and radiation therapy (N = 4) (Tables 1 and 2). Chromosomal analysis revealed chromosomal translocation (15; 19) in 1 patient with nasopharyngeal CA (patient 1, Table 1) and 1 patient with laryngeal CA (patient 6, Table 1); this translocation was not detected in any of the other 5 patients. The 5 patients without translocation (15;19) responded well to treatments and are all disease-free with a mean follow-up of 47 months (range, 4 to 116 months) (Tables 1 and 2). However, patients 1 and 6 with chromosomal translocation (15;19) both died of their disease with a mean survival of 6 months (range, 3 to 9 months) (Table 1, 2).

Patient 1 was a 12-year-old otherwise healthy female who was referred for evaluation of a per-

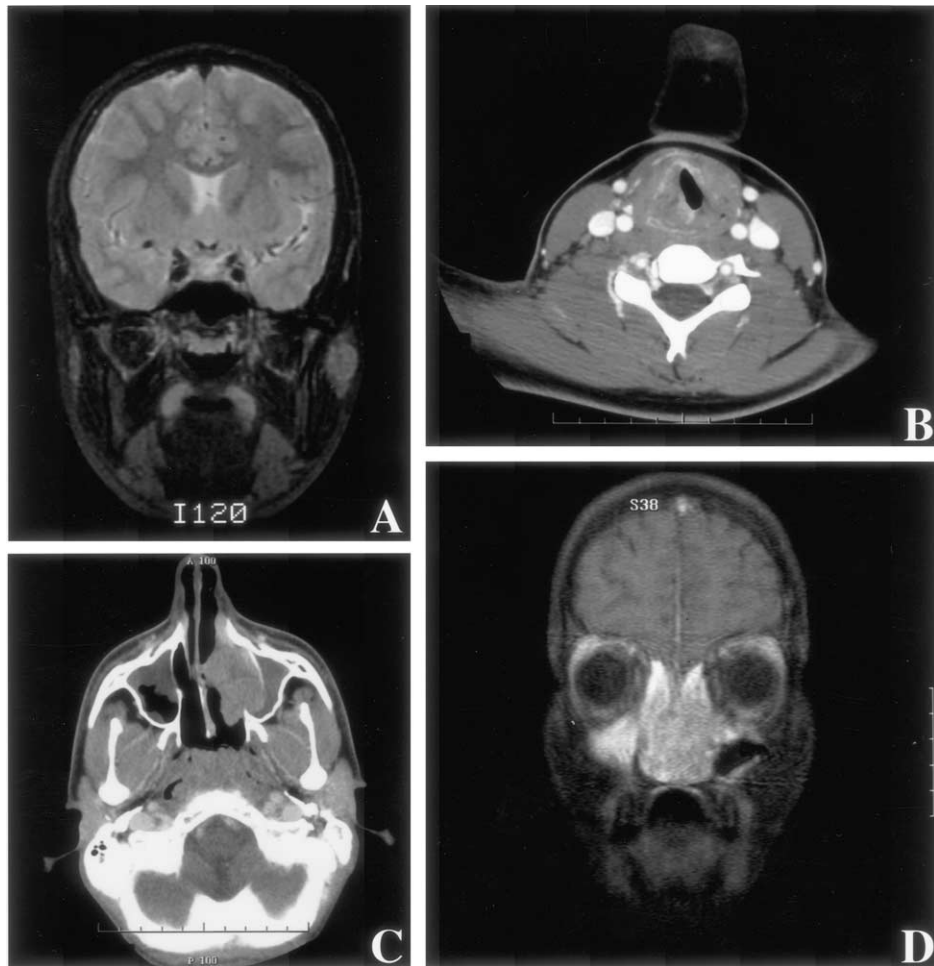


Fig 1. **A**, Coronal fast spin echo inversion recovery image demonstrates a rounded parotid tumor; **B**, axial contrast-enhanced CT demonstrates a poorly defined mass involving the right side and posterior aspect of the larynx; **C**, axial contrast-enhanced CT reveals an enhancing tumor located within the left nasal cavity with remodeling and erosion of the medial wall of the left maxillary antrum; **D**, coronal fat-suppressed T1 weighted MR image reveals intensely enhancing sinonasal tumor.

sistent nasal congestion and obstruction despite antibiotic use. She had a negative medical and social history. Her examination was only significant for a nasopharyngeal mass. As part of her work-up she underwent a CT scan and MRI; these revealed a mass occupying the nasopharynx, nasal cavity, and sphenoid sinus with erosion of bone of the sphenoid sinus and intracranial extension (Fig 2). Extensive evaluation including chest CT, abdominal ultrasound, and bone scan did not show any evidence of metastasis. Results of the laboratory analysis for Epstein-Barr virus were negative by serology and polymerase chain reaction. Results of the biopsy of the nasopharyngeal mass were consistent with poorly differentiated CA (Fig

3). She was started on chemotherapy per adult Protocol 99-052 Regimen A for nasopharyngeal CA. Four weeks after initial presentation she presented with loss of vision in her right eye. She was started on dexamethasone, carboplatin chemotherapy, and radiation. Soon after, she developed bony metastases to the femoral head, sacrum, iliac spines, and vertebral bodies. She died 3 months after diagnosis despite aggressive treatment. Autopsy was not done in accord with the family's request.

Patient 6 was a 13-year-old white female without any significant medical or family history who was referred with a 6 to 8 week history of progressive sore throat, dysphagia, hoarseness, and a

Table 2. Treatment

Patient	Sequence of treatment
1	1) Adult Protocol 99-052 Regimen A 2) Dexamethasone/Carboplatin with XRT (6000 cGy)
2	1) 3 cycles: Vincristine/Cytoxan/Doxorubicin 2) 3 cycles: Adriamycin/VBIO/Carboplatin
3	3) Resection via degloving approach 1) Resection via mandibulotomy approach 2) 3 cycles: Cisplatin/5FU with concomitant XRT (5580 cGy)
4	1) Parotidectomy and supraomohyoid neck dissection
5	1) Parotidectomy
6	1) Tracheostomy 2) 3 cycles: Docetaxel/Cisplatin/5FU 3) XRT (5400 cGy) 4) Neck dissection 5) Palliative Chemotherapy
7	1) Tracheostomy and G Tube 2) 3 cycles: Cisplatin and concomitant XRT (6000 cGy)

left neck mass despite antibiotic use. There was no history of alcohol or tobacco exposure. Her evaluation, prior to our assessment, included group A streptococcus, Epstein-Barr virus, and thyroid function tests with normal results. Physical examination was significant for a 2 × 3 cm firm mass in the left neck (level III), a large irregularly shaped mass involving the epiglottis obstructing the glottic inlet, and decrease vocal cord mobility on the left side (Fig 4). Biopsy findings were consistent with poorly differentiated SCCA (Fig 5). A CT scan of the neck confirmed multiple lymph nodes on the left side measuring 1 to 3 cm. A CT scan of the head, chest, and abdomen, and bone scan revealed no abnormalities. The patient underwent a tracheotomy and gastrostomy tube placement and was started on chemotherapy (docetaxel, cisplatin, 5-fluorouracil, leucovorin). After the completion of the third cycle of chemotherapy, she underwent a repeat endoscopy, which revealed an excellent response. Biopsy of the larynx demonstrated a lack of residual tumor. A repeat CT scan of the neck revealed decreased neck adenopathy. The patient underwent radiotherapy of the neck to 5400 cGy and boost to the larynx to 6900 cGy. After completion of radiation therapy, she under-

went direct laryngoscopy and neck dissection. Results of a laryngeal biopsy were negative; however, she had a tumor present within 1 of the 30 cervical lymph nodes. Two months later, she presented with a neck mass that was deemed unresectable. She died of respiratory distress as a result of severe swelling of head and neck despite further chemotherapy 9 months after presentation. Post-mortem examination revealed residual poorly differentiated SCCA involving the epiglottis and supraglottic area. The tumor was also identified in the skin of the neck and the thorax.

DISCUSSION

Head and neck cancer is 100 times more common in adults than in children and represents less than 1% of the approximately 900,000 new cases of cancer reported annually in the United States.⁹ SCCA is most common in adults; lymphoma and rhabdomyosarcoma predominate in children.¹⁰ Childhood SCCA is rare and has been histologically classified as differentiated CA, undifferentiated CA, and lymphoepithelioma.¹¹ Within the respiratory system the nasopharynx, larynx, and trachea are the most common sites of SCCA in children. It has been estimated that 90% of adult head and neck SCCA can be attributed to tobacco and alcohol usage. These factors are usually absent in children. However, predisposing factors such as epidermolysis bullosa, xeroderma pigmentosa, respiratory papillomatosis, and history of head and neck radiation are of consideration in childhood SCCA.

Finding the gene, abnormalities within a gene, and elucidation of the molecular disorder underlying a particular illness is a powerful approach to further our understanding of the disease process. Characteristic recurrent translocations are common in hematopoietic neoplasms and sarcomas. This has allowed for some highly effective therapies based on changes of the cell biology associated with the translocations. For example, chronic myeloid leukemia is characterized by a translocation (9;22) fusion gene encoding the BCR-ABL oncoprotein causing constitutive ABL tyrosine kinase activity. This finding has resulted in dramatic therapeutic responses using the ABL ATP-binding pocket inhibitor.

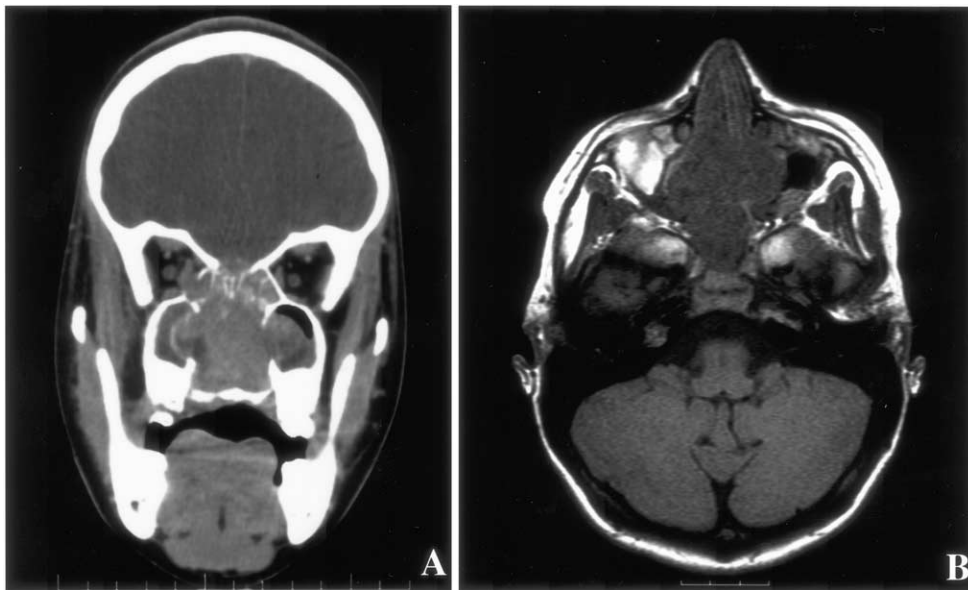


Fig 2. A, Coronal contrast-enhanced CT demonstrates heterogeneously enhancing tumor filling the nasal cavity with erosion of the medial walls of the maxillary antra and extension through the anterior cranial fossa. Obstructed secretions are present in the paranasal sinuses. **B,** axial T1-weighted MR image without contrast reveals the extensive sinonasal tumor.

Table 3. Patients: Carcinoma with translocation (15;19)

Age years	Sex	Presentation	Location	Karyotype	Metastasis at presentation	Treat- ment	Survival (weeks)	Author
11	F	Shoulder pain	Intrathoracic	t(15;19)(p12;q13)	Yes	C, R	18	Kee et al 1991
22	F	Chest pain	Mediastinum	t(15;19)(q15;p13)	No	C, R	16	Kubonishi et al 1991
		Superior vena cava syn- drome	Thymus					
5	M	Superior vena cava syn- drome	Mediastinum	t(15;19)(q12;p13.1)	Yes	C	6	Lee et al 1993
34	F	Not specified	Lung	t(15;19)(q11;p13)	Yes	Not specified	Not specified	Dang et al 2000
13	F	Hoarseness	Larynx	t(15;19)(q13;p13.1)	No	C, R, S	36	Vargas et al 2001
12	F	Nasal ob- struction	Nasopharynx	t(15;19)(q13;p13.1)	No	C, R	13	Vargas et al 2001

C, Chemotherapy.

R, Radiation therapy.

S, Surgery.

Most clinically aggressive carcinomas have complex karyotypes and characteristic recurrent chromosomal translocations have not been identified with the exception of thyroid and papillary renal cell CA [1,2]. However sporadic abnormalities such as chromosome 15 have been reported in thymoma and SCCA of head and neck.^{12,13} Ab-

normalities of chromosome 19 have been reported with familial thyroid tumor, anaplastic thyroid carcinoma, seminoma, and parathyroid carcinoma.¹⁴⁻¹⁷ Translocations between 19p13 and chromosome 1 in meningioma and translocation involving the breakpoint 19p13.1 in Warthin's tumor have also been reported.^{18,19}

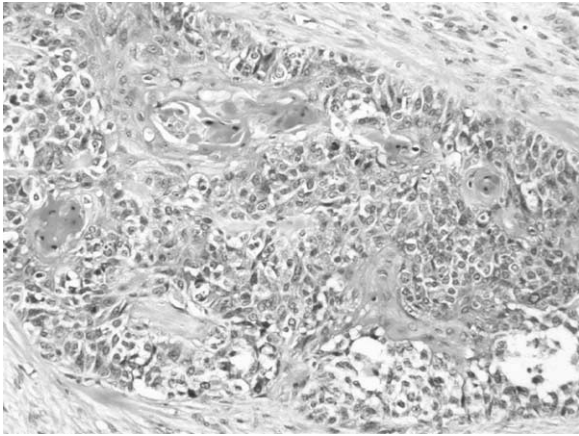


Fig 3. Nasopharyngeal mass; histology consistent with poorly differentiated carcinoma.

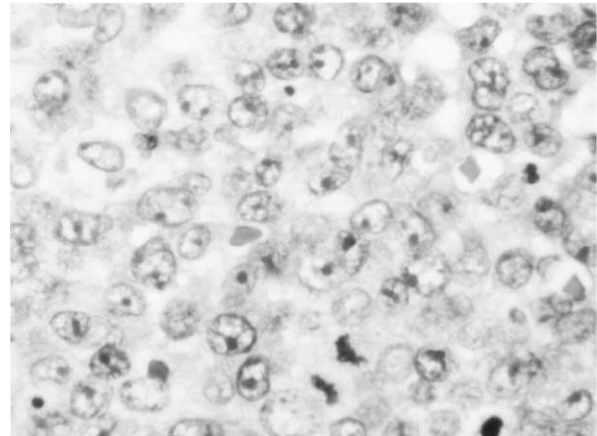


Fig 5. Laryngeal mass; histology consistent with poorly differentiated squamous cell carcinoma.



Fig 4. Endoscopic evaluation of the larynx: mass involving the epiglottis obstructing the glottic inlet.

Translocation (15;19) is the first recurring translocation identified in a particularly aggressive form of carcinoma. In 1991 Kees et al⁴ reported the first case of translocation (15;19) in an 11-year-old female with intrathoracic carcinoma. Since the initial report only 5 other cases, including 2 of our cases have ever been reported.³⁻⁷ The reported cases include 5 females and 1 male with mean age of 16 years (range, 5 to 34 years) (Table 3). The location of the carcinoma ranged from mediastinum (N = 2), intrathoracic (N = 1), lung (N = 1), nasopharynx (N = 1), and larynx (N = 1). Follow-up was reported in 5 patients. These patients died of their disease in 6 to 36 weeks (mean, 18 weeks) after initial presentation despite aggressive treatment (Table 3).

The precise cell of origin for aggressive carcinoma with t(15;19) is unknown. Previous authors³⁻⁶ have suggested various possible origins including thymus, lung, and germ cell. Our 2 patients with t(15;19) both had tumors arising in the upper respiratory tract (larynx and sinonasal region). Adding these 2 cases to the previously reported CA, the overall best explanation for the histogenesis of this neoplasm is that the CA arises from cells of the upper airway epithelium, probably the submucosal gland.⁷ The t(15;19) translocation may be under recognized because it occurs in carcinomas, which often do not grow well in cultures, precluding cytogenetic evaluation by standard karyotyping methods. With the development of adjunctive methods for cytogenetic evaluation of specific abnormalities, further investigation of carcinomas of other sites is possible.⁸

It remains unclear how the translocation t(15;19) contributes to the pathogenesis of aggressive upper respiratory tract carcinomas of childhood. Theories such as activation of Notch3, a gene located on 19p and involved in cell differentiation and regulation of the cell cycle; and disruption of E2A, a gene located specifically at 19p13 that codes for immunoglobulin kappa enhancer factors were previously postulated.^{3,15} Investigation of cell lines from one of our patients has led to the discovery of interruptions in the coding sequence of the BRD4 bromodomain gene at 19p.⁸

All reported 6 patients with t(15;19) showed aggressive clinical presentations and a fatal course of disease. Although the majority of tumors have

occurred in females, the number of cases is too small to indicate a statistically significant female predominance.

Due to scarcity of carcinoma of the aerodigestive tract in children, treatment protocols are not well established. Initial aggressive surgery, radiotherapy, and chemotherapy may be warranted. Despite advances in craniofacial and skull base approach, surgical resection remains challenging. Also, the long-term effects of chemotherapy and higher incidence of postirradiation complications in the pediatric age group is of major concern.

Based on the reported cases and our findings, it appears that chromosomal translocation (15;19) in patients with CA of upper aerodigestive tract may indicate a poor prognosis despite aggressive multimodality treatment. Further investigation is needed to better understand the cause and relationship of the translocation (15;19) and aggressive behavior of these tumors and may help us guide in establishing more effective treatment protocols.

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