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Review Article

Childhood carcinoma larynx

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Abstract

Carcinoma Larynx is very rare in children and adolescents. Only few cases of childhood and adoloscent Carcinoma Larynx has reported worldwide. Exact cause of childhood and adoloscent Carcinoma Larynx is not known but few risk factors have been detected. Childhood and adolescent carcinoma Larynx is diagnosed delayed and its outcome is usually fatal. Earlier suspicion, accurate diagnosis and prompt intervention are essentially recommended.

Introduction

Malignant tumours of larynx is rare in children and adolescents, most of which tend to be derived from mesodermal tissue. In a recent review by Fertilo et al. 47 cases of laryngeal cancer were identified in children and adolescents with the most common malignancy being rhabdomyosarcoma (42%) then squamous cell carcinoma (27.6%), and then other rare tumors including synovial sarcoma, malignant fibrous, histiocytoma, Non-Hodgkins lymphoma, chondrosarcoma, Ewing sarcoma, fibrosarcoma, malignant schwannoma, mixed sarcoma, and mucoepidermoid carcinoma.[1] Squamous cell carcinoma of larynx is extremely rare in adoloscents and children but has a typically aggressive nature and fewer than 75 cases of squamous cell carcinoma has been reported in paediatric population upto date.[2] In patients less than 15 years of age, laryngeal cancers accounts for less than 0.1% of all head and neck malignancies;[3,4,5] and only 22 cases in patients 10 and younger group and 63 cases in patients 15 and younger group have been reported upto date since 1868. The first documented case of laryngeal cancer in a child was reported by rehn in 1868 in a 3 year-old child[5]. Childhood and adolescent carcinoma larynx is found more among the low socioeconomic group in the developing countries[6,7] with more female prevalence rate (40% of childhood cases vs less than 10% adult cases[1]).

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Case review

Carcinoma larynx is 4:100000 in UK whereas it is 10:100000 in India and Africa and it is twice common in socioeconomical class v than in class 1.[6] One report suggests that 66% patients are of low socioeconomic group.[7] Childhood and adoloscent carcinoma larynx is more commonly supraglottic carcinoma

Carcinoma larynx is an old-age malignancy; the most age at presentation of carcinoma larynx is around 7th decade.[8] In Pakistan, the lowest age reported is 20 years, in Ghana, the lowest age reported is 17 years, in Bangladesh the lowest age reported is 35

years- but recently a case of 10 years- old girl has been reported,[9] in India, the lowest age reported is 6 years-old[10], in USA carcinoma larynx in 15 years old[1,11] child has been reported; Childhood and adolescent carcinoma larynx has been also reported in 13.5 years old, 13 years old, 12 years old, 11 years old, 9 years old, 8.5 years old, 6 years old including the first case in the 3 years old child has been reported worldwide.

Glottic carcinoma is the common carcinoma larynx in western countries. In UK, it is 40% and in USA it is 30% [6] but supraglottic carcinoma is the commonest type in Indian subcontinent [7]. Supraglottic carcinoma is found more among the younger age group in the low socioeconomic class with less male/ female ratio in the developing countries.[6,7] However, the incidence of female patients is higher in childhood (40% of childhood cases vs. less than 10% of adult cases).[1] Worldwide, Vocal folds are the most common site of involvement by squamous cell carcinoma in adoloscents and children followed by supraglottic and then subglottic sites.[12] 90% laryngeal carcinoma is histopathologically SCC and its variant.[8]

Risk factors, except previous irradiation of papillomas, papillomatosis, malnutrition, are rare. Adolescent carcinomas also appear to be linked to immunologic and genetic factors rather than more common risk factors such as tobacco use, previous radiation, and chemical carcinogens found in adult patients.[13,14] Among the other reported risk factors for laryngeal carcinoma in children and adolescents are papillomatosis of the larynx, laryngopharyngeal reflux, human immunodeficiency virus (HIV) infection (<45 years- old),[1] immunosuppressive therapy, exposure to drug use during pregnancy, both active and passive smoking, exposure to certain chemicals (e.g. asbestos), alcohol use, poor oral hygiene, geographical and socioeconomic status[6] and a family history of cancer[15] Malignant degeneration can take place in juvenile papillomatosis which was found by Rabbett (1965) to be more common in children who had had radiotherapy for papillomatosis, consequently the practice of irradiating these children has been abandoned.[4] The relationship of HPV to laryngeal carcinoma is unclear although some studies have attributed laryngeal irradiation as a predisposing factor in the development of carcinoma- HPV induced genome mutation and chromosomal translocation also have been reported. Until the 1970s, malignant degeneration of RRP was seen in association with patients that underwent radiation therapy for their disease. Spontaneous malignant degeneration of RRP has been reported in the laryngotracheal and bronchioalveolar regions with an incidence rate of 2.3%.[16] Malignant transformation of papillomatosis was 14% (6 of 43 irradiated cases) before 30 years of age whereas no transformation was reported in 58 similar cases treated with surgery alone[17]. Younger patients with aggressive malignancy may have an underlying genetic or immune defect, bleomycin-induced chromosomal breaks also has been reported in patients under 30 years.[15]

Younger patients tend to have a long history of progressive airway obstruction, dysphagia, or dysphonia which may or may not necessitate tracheostomy and/or nasogastric tube feeding; but lesions are not recognized until an otolaryngologist is consulted for a fiberoptic airway examination. Other symptomes may include hoarseness or cough, which may be mistaken for common respiratory infections, prepubertal voice change, or other benign childhood conditions. Indirect laryngoscopy may reveal the clinical findings but the diagnosis is confirmed by direct laryngoscopy which helps the staging

of the lesion and performing the biopsy. A delay in diagnosis can be attributed to the erroneous attribution of voice changes to puberty, recurrent respiratiory tract infection or asthma, vocal abuse and difficult examination in children which makes the case more aggressive and ultimately fatal.[13,14] Due to its rarity, tendency to mimic benign conditions and the relative difficulty of the pediatric laryngeal examination, SCC is not usually considered in the differential diagnosis of persistent hoarseness or cough, which may lead to a delay in diagnosis. The differential diagnosis of laryngeal neoplasm in children includes: papillomas, subglottic hemangiomas, squamous carcinoma, rhabdomyosarcoma, and adenocarcinoma of minor salivary gland.

The scarcity of cases, attempt to preserve anatomy and function of larynx and for avoidance of complications impedes establishment of treatment protocols in children. All authors agree that a primary work up should consist of detailed radiologic imaging endoscopy with biopsy, and possible tracheostomy for airway protection and, thereafter, definitive management of squamous cell carcinoma in pediatric patients has varied based on the individual circumstance of the patient. Overall, the management of children with laryngo-pharyngeal carcinoma remains a challenge because psychosocial aspects are also associated. It is more difficult to explain to young patients the nature of their disease, the type of treatment that is going to be performed, and it's after effects.

Prognosis of childhood laryngeal cancer is unclear since the reported survival rates are not tumor stage related. The earlier was the age at presentation, the 5-year relative survival rate was proportionally less. Researchers have also looked at age at the time of the onset of papillomatosis, the different types of human papillomavirus, infection with multiple viruses, histopathologic features, and immunohistochemical measures of cell proliferation for evaluation of the prognosis.[15] Recently, studies have suggested that prognosis may be affected by the presence of chromosomal translocation 15:19 or of human papillomavirus (HPV) DNA within tumour cells[2]. Regarding HPV sub typing, HPV 11 had been linked to the malignant transformation of juvenile-onset RRP[18]. HPV-16, 6, 18, 33, 35, 58 are also the common subtypes involved. Rate of HPV positivity in carcinoma larynx is 13% - 50% in different series and HPV-16 is the most frequently isolated subtype.[2] Co-infection with HPV 16/18, 18/33, and 6/33, 16/33, and 6/18 has been reported which is common in immune-deficiency since it impairs the control of HPV infection.[3] Specific oncogenes (E6 and E7) within the DNA sequence of HPV that can determine the aggressiveness of the clinical presentation.[19] High-risk HPV alters the tumour suppressor gene P^{16} resulting over expression of P^{16} (INK-4a) protein,[20] therefore, P^{16} immunostaining of tumour nuclei and cytoplasm serves as a marker of HPV positivity. In HPV-negative lesions, downregulation of p^{16} has been correlated with increased dedifferentiations, more locally advanced stage, and tendency for radiotherapy failure in laryngeal SCC.[21] Translocation (15:19) results in a BRD4-NUT fusion oncogene, which likely disrupts the normal BRD4 function of regulation of cell cycle progression, and it is clinico-pathologically characterized by young age, female predilection, midline carcinoma of the neck or upper thorax, and a rapidly fatal course[20], and is suggests that this entity arises from thymic or respiratory epithelium and is very unresponsive to aggressive chemoradiotherapy and is commonly lethal, and its presence indicates a poor prognosis despite aggressive multi-modality treatment

(one study reported that carcinoma larynx with translocation got a mean survival of 6 months, compared to carcinoma larynx without translocation were disease free at a mean follow-up of 47 months) and another study reported that 43% carcinoma larynx with translocation had poorly differentiated carcinomas[21]. Detection of HPV DNA types 6, 11, 16, 18, 31, 33, and 51 was performed by in situ hybridization, with confirmation by polymerase chain reaction. Immunohistochemical staining with p[16] shows diffusely positive staining in the tumor cells. Dual-color FISH assays were performed to evaluate chromosomal translocation (15:19).[22]

Discussion

Childhood and adolescent carcinoma larynx is commonly due to HPV infection in patients with malnutrition, immunedeficiency and other environmental oncogenic factors which are common epidemiological features of developing countries. We reported a case of 10 years-old malnourished girl with persistent and progressive sore throat, dysphagia, dysphonia and ultimately respiratory distress necessitating tracheostomy and nasogastric tube feeding which was staged as $T_2 N_0 M_0$ and biopsied under direct laryngoscopic examination and this first case of childhood carcinoma larynx ever reported in Bangladesh[9] was diagnosed histopathologically as SCC; she was referred to avail radiotherapy but could not afford availing the appropriate treatment due to different socioeconomical constrains and ultimately embraced the unfortunate fatal outcome. The management of childhood carcinoma larynx is more difficult than in adults because of aggressive nature due to delayed diagnosis, delicate pediatric anatomic structures, and long-term complications following treatment including psychosocial factors specific to adolescents. So, accurate and early recognition and diagnosis of the disease is of therapeutic importance because of its aggressive nature, potential for associated complications and frequently poor outcome.[15] Underlying genetic and immunedeficiency makes the clinical nature of disease more aggressive.[15] Long-term complications of local therapy are important in young children but definitive local therapy is essential for a tumor control. Long-term follow-up will be important for these patients since there are at an increased risk for radiation-induced endocrinological deficiencies, arrested growth of irradiated tissues, and for the development of second malignancies.[2] HPV testing should be considered for these patients since it has both prognostic and potentially therapeutic implications and for this reason, vaccination may be considered and requires further investigation.[2]

Conclusion

Childhood laryngeal carcinoma is a very rare malignant condition. The aetiology of this disease is not exactly known. Clinical features are aggressive and the outcome is poor since the diagnosis and the treatment is always late. In any suspected cases where some risk factors are associated should be dignified. Although unusual, one should have a high index of suspicion for any hoarseness, cough, or upper airway disease that does not respond to appropriate medical treatment. Accurate and early diagnosis of the childhood laryngeal carcinoma with prompt aggressive treatment is essential. By reporting this case and highlighting the difficulties in diagnosis and treatment we hope that negligence of children patients with sore throat along with voice change should be decreased. The motive of this review article is to increase clinical awareness which may lead to an improved outcome of the patients of childhood and adolescent carcinoma larynx.

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