

Nasal and nasopharyngeal Burkitt's lymphoma in pediatric age group – A review

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ABSTRACT

Burkitt's lymphoma (BL) is an aggressive variety of non-Hodgkin's lymphoma where a neoplastic monoclonal proliferation of the lymphoid cells occurs at the site of the immune system. BL is commonly related to human immunodeficiency virus infections, EBV infections, and malaria-endemic region. BL at the nasal cavity and nasopharynx in pediatric age is extremely rare and often spread to the skull base and brain rapidly. It often presents with non-specific symptoms which lead to misdiagnosis and delayed treatment. The symptoms of pediatric patients with nasal and nasopharyngeal BL are range from obstruction of the nasal cavity to recurrent nasal bleeding, headache, and facial pain. The diversity of the symptomatology of this clinical entity is mostly associated with the anatomical location of this tumor. Late diagnosis or misdiagnosis usually causes a fatal outcome. Hence, early identification and treatment improve the prognosis of pediatric nasal and nasopharyngeal BL. Histopathology and immunohistochemistry usually confirm the diagnosis. This aggressive and rapidly growing lymphoma is curable and highly sensitive to chemotherapy. Early diagnosis and prompt treatment are the important aspects of preventing complications and curing BL. This review article aims to discuss the nasal and nasopharyngeal BL in pediatric age including its epidemiology, etiopathology, investigations, and current treatment. It will also catalyze additional studies for BL.


Key words: Burkitt's lymphoma, Chemotherapy, Nasopharynx, Pediatric age

Burkitt's lymphoma (BL) is a high-grade B-cell lymphoma that was first documented by Denis Burkitt, a British surgeon in the mid part of the 20th century in equatorial African children [1]. BL is a B-cell lymphoma with a short doubling period and often results in an enormous tumoral mass [2]. BL is considered as fastest growing human neoplasm with a cell doubling time of 2–48 h [2]. BL is the first pediatric tumor that responds to chemotherapy alone. It was the most common pediatric cancer found in the region where malaria is holoendemic such as Brazil, equatorial Africa, and Papua New Guinea [3]. Approximately 58% of the BL in the head-and-neck region affects the mandible or maxilla [3,4]. Because of the rarity of the primary nasal and nasopharyngeal BL in childhood and its non-specific clinical presentations, the diagnosis is often late or misdiagnosed because of initial thinking of benign etiologies. A timely and accurate diagnosis of BL is challenging but crucial [5]. The standard treatment of BL in pediatric age is chemotherapy but sometimes radiotherapy or surgery may be added [6]. There

are very few reports for nasal and nasopharyngeal BL in the pediatric age available in the medical literature.

METHODS FOR LITERATURE SEARCH

Research articles regarding the pediatric nasal and nasopharyngeal BL were searched through multiple approaches. We started by searching the Scopus, PubMed, Medline, and Google Scholar databases online. A search strategy using Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines was developed. This search strategy recognized the abstracts of published articles, while other research articles were discovered manually from the citations. Randomized controlled studies, observational studies, comparative studies, case series, and case reports were evaluated for eligibility. There were a total number of articles 76 (22 case reports; 24 cases series; and 30 original articles) (Fig. 1). This article reviews the epidemiology, etiopathology, clinical profile, investigations, and current treatment options of pediatric nasal and nasopharyngeal BL. This review article presents a baseline from which further prospective trials can be designed and which may help as a spur for further research in this rare clinical condition for which very few studies are performed.

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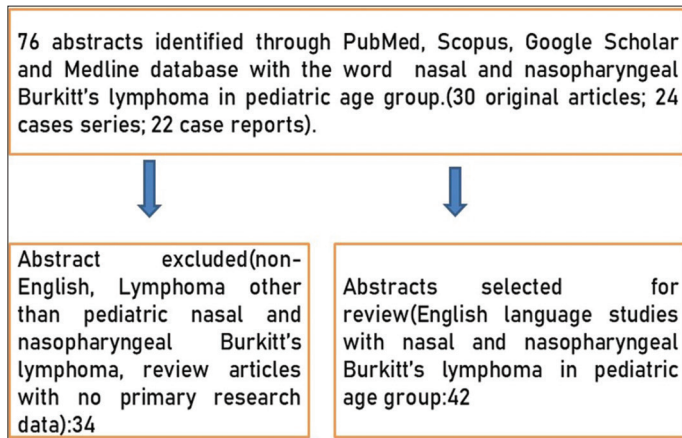


Figure 1: Flow chart showing methods of literature search

EPIDEMIOLOGY

The first case of BL was documented in 1958 after assessing the children with rapidly growing tumors of the jaw [7]. BL accounts for approximately 40% of the non-Hodgkin's lymphoma in pediatric age and it accounts for <5% in young adult age [8]. Africa and New Guinea represent the region of holoendemic malaria and early acquisition of Epstein Barr virus (EBV). The yearly incidence is approximately 40–50/million children younger than 18 years [9]. Half of the childhood BL is found and approximately 90% of the lymphoma is diagnosed in the endemic regions. The sporadic type of BL is usually seen in pediatric ages of 3–12 years and is 3.5 times more common among boys than girls [10]. Sporadic variety of BL is often seen in the low-risk region such as North America, Northern and Eastern Europe, and the Eastern region of Asia with an annual incidence of 2/million pediatric populations <18 years of age [10]. Immunodeficiency-associated BL often occurs with an incidence of 22/100,000 people per year in the United States [11].

ETIOPATHOLOGY

BL was the first tumor associated with the virus as an etiological agent. This was the first tumor associated with chromosomal translocation which stimulated the oncogene. This was the first tumor associated with human immunodeficiency virus (HIV) infection. The etiology for BL includes chromosomal translocation t (8; 14) (q24; q32) and deregulation of the c-myc oncogene [12]. The overexpression of the c-myc has been found to activate apoptosis through p53 dependent pathway in normal B-cells. Several cases of BL have mutations of the tumor suppressor gene and Tp53, which can override the apoptotic mechanism of the cells. A p53 dependent pathway can be circumvented through the downregulation of proteins of the cells, called BIM which acts as an antagonist to the anti-apoptotic protein, Bcl-2 [13]. There are also associated etiological factors of BL such as EBV infection and malaria [13]. There are three varieties of BL which include endemic, sporadic, and immunodeficiency [13]. Several reports support the causative role of EBV etiological agent for BL. Initially,

it was hypothesized that BL was associated with an arthropod-borne infectious agent, due to its geographical distribution and clinical factors [14]. In 1964, Epstein *et al.* identified herpes virus-like particles in a cell line from BL biopsy which was later on called EBV (also called human herpes virus-4). The etiological link between BL and EBV was confirmed by the elevated antibodies to EBV antigens in BL patients [15]. The EBV induces the immortalization of the B-cells in culture [16]. A raised antibody titer is often detected before the development of the origin of the tumor [15]. BL occurs in HIV patients with raised CD4 T-cell numbers, which suggests that immunological suppression is not the alone etiology of this malignancy. Prolonged antigenic stimulation of the B-cells as in plasmodium falciparum infection or long-standing HIV infection might be the pathologic mechanism for endemic and HIV-associated BL. HIV patients with BL have increased serum levels of soluble CD30 and CD23 markers of B-cell activation before the origin of the BL [17]. Patients having HIV viremia even under treatment with antiviral treatment show a higher risk for developing the HIV-associated BL than those with unmeasurable loads of the virus [18].

As per the WHO classification, there are three types of BL such as endemic, sporadic, and immunodeficiency-associated varieties [19]. Endemic BL type refers to African pediatric patients, often 4–7 years of age, and involves jaws, kidneys, ovaries, gastrointestinal tract, breast, and extranodal sites [20]. EBV is usually seen in endemic types. Sporadic types of BL can occur worldwide where the cases are associated with no specific climatic or geographic region. In sporadic variety, the abdomen is commonly affected followed by kidney, ovaries, and Waldeyer's ring. Immunodeficiency-associated BL is seen in HIV patients and is also associated with allograft recipients and persons with congenital immunodeficiency [21]. From a pathology standpoint, there are several differential diagnoses which include other varieties of high-grade B-cell lymphoma, blastoid mantle cell lymphoma, lymphoblastic lymphoma, and leukemia [22]. Myc rearrangement is not very specific for BL [23]. Other varieties of high-grade non-lymphomatous childhood malignancies are also considered such as embryonal rhabdomyosarcoma, metastatic neuroblastoma, Ewing sarcoma, and primitive neuroectodermal tumor, as all of them show a diffuse proliferation of small to medium-sized cells.

CLINICAL PRESENTATIONS

BL is not the only worrisome clinical entity where the presenting clinical manifestations may look benign. BL is usually seen among children and young adults and rarely in the adult age group. It is more common in males than females with a male to female ratio of 2:1 [24]. In the endemic region, BL often affects the facial bones such as the jaw, orbit, and maxilla [25]. There are varied clinical manifestations in the BL. BL is considered a rapidly spreading malignancy that easily spread to the skull base region from the nose and nasopharynx. The common clinical manifestations of nasopharyngeal BL are nasal blockage, nasal

bleeding, rhinorrhea, hyponasal speech, facial pain, neck swelling, headache, and otological symptoms such as ear pain, fullness in the ear, deafness, and tinnitus [26].

In the adolescent age group, recurrent nasal bleeding and nasal block may give suspicion of nasopharyngeal angiofibroma. The patient may present with sinusitis and headache. The sinusitis in nasal and nasopharyngeal BL is due to blockage of the drainage pathways of the paranasal sinuses. Serous otitis media or glue ear is a common clinical presentation in this patient. The headache of the patient may be due to intracranial extension of the nasal and nasopharyngeal BL where the lesion is extended into the sphenoid sinus with extradural intracranial extension. The serous otitis media and hearing loss in pediatric patients with nasal and nasopharyngeal BL are due to obstruction of the nasopharyngeal opening of the Eustachian tube by the BL. The ocular manifestations include eye pain, ptosis, and visual changes. The patient may be presented with visual loss due to the involvement of the optic nerve by the tumor mass at the orbital apex. In the case of BL in the head-and-neck region, the symptoms are swelling of the jaw, facial swelling, proptosis, and loosening of teeth [27]. Patients may present with cervical lymphadenopathy specifically submandibular lymph node swelling and anterior cervical lymphadenopathy.

INVESTIGATIONS

Prompt diagnosis of BL is vital for preventing the widespread dissemination of the tumor and compressing the vital structures near the nose, nasopharynx, and skull base [28]. Persistent nasal blockage and nasal bleeding require flexible nasopharyngolaryngoscopic examination to find out any mass in the nose and nasopharynx. X-ray nasopharynx with the lateral view will show the mass at the nasopharynx. Ultrasound of the abdomen and X-ray of the chest in the initial part will provide any evidence of the lesion. Computed tomography (CT) and magnetic resonance imaging (MRI) are two useful investigations for evaluating the site and extent of the neoplasm (Fig. 2). CT scan will rule out any bony erosion at the nasopharynx and skull base. CT scan of the chest, abdomen, and pelvis can be done to rule out any lesions in the abdomen such as liver, kidney, and pancreas. Positron emission tomography (PET) scan is helpful to find out any hypermetabolic sites in the body such as the head-and-neck region, chest, abdomen, and pelvis. CT scan, MRI, and PET scan are helpful for complete workup in pediatric patients with nasopharyngeal BL. Imaging the chest is also useful for the proper evaluation of BL patients. The imaging of the chest is done to rule out lymphadenopathy in the chest. CT scans of the chest and abdomen are useful to rule out any mass or lymphadenopathy. A PET scan can be recommended but is not essential always.

The diagnosis of BL is usually based on histopathological study and immunohistochemistry. Endoscopic biopsy is usually taken from the nasal and nasopharyngeal mass under local or general anesthesia. The histopathological study shows neoplastic lymphoid cells with round nuclei, multiple small nucleoli, dispersed chromatin, and a small amount of amphophilic cytoplasm

(Fig. 3). The mitoses are numerous and the neoplastic cells are admixed with tangible body macrophages, which are nothing but macrophages phagocytosing apoptotic debris, giving a “starry sky” pattern. The majority of the BLs are immunoreactivity for surface immunoglobulin M (IgM), pan-B cell antigens including CD19, CD20, and CD22, and coexpress CD10, CD43, and BCL6 but not CD5, CD23, BCL2, or TdT [29]. The nuclear staining with c-myc antibody is positive in all patients of BL whereas translocation exists between the c-myc gene and IgH gene in 80% of cases or with either lambda or light chain, seen in the rest 20% of cases [30]. All cases of BL show positive for Ki-67. The antibody titers for EBV are positive in almost 100% of cases with endemic BL whereas this is only positive in 15–30% of the patients with sporadic BL [31,32].

As this neoplasm is aggressive and spread rapidly, it is essential to get a prompt diagnosis and prevent the compressive effect on the vital structures at the nasopharynx and skull base region or prevent widespread dissemination. There are few essential investigations done in patients of BL such as full blood count, differential count, blood film, erythrocyte sedimentation



Figure 2: Magnetic resonance imaging of the head-and-neck area shows a large nasopharyngeal homogeneously enhancing mass with intracranial extension

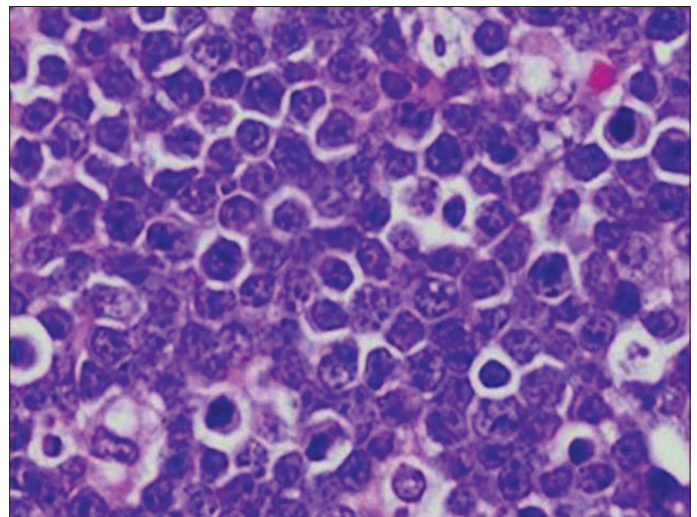


Figure 3: Histopathological picture of Burkitt's lymphoma

rate, urea, electrolytes, liver function tests (bleeding parameters of prothrombin time and partial thromboplastin time and D-dimers) to assess the liver and kidney involvement, serum lactate dehydrogenase, and urate measurement to assess the turnover of the tumor. Lumbar puncture and bone marrow biopsy can also be done. Once the diagnosis is confirmed, bilateral bone marrow aspirates, trephine cores, and cerebrospinal fluid analysis can be done to rule out any malignant cells [33].

TREATMENT

BL is a rapidly spreading tumor and leads to serious health problems. Hence, the pediatrician or pediatric otolaryngologist or pediatric oncologist should do a timely diagnosis for prompt and appropriate treatment. Pediatric patients with nasal and nasopharyngeal BL may receive systemic and intrathecal chemotherapy regimens. The treatment of BL typically includes intermittent high dose chemotherapy of cyclophosphamide, vincristine, doxorubicin, and methotrexate. Rituximab (monoclonal CD20 antibody) gives a promising result when added with chemotherapeutic agents [34]. The debulking of the tumor is helpful as an adjunct therapy where the anatomical site permits it; however, the role of the debulking has not been studied well [35]. When the prognosis is poor, locoregional radiation therapy plays an important role in providing local control of the symptom [36,37].

The treatment includes surgery, chemotherapy, and highly active antiretroviral therapy. BL patients are highly sensitive to chemotherapy and so patients should be immediately referred to the pediatric hemato-oncology. The chemotherapeutic agents include methotrexate, vincristine, cyclophosphamide, doxorubicin, and cytarabine [38]. Early stages of BL respond well to chemotherapy. However, the delayed stage of the tumor, the advanced age of the patient, and the high tumor burden at the time of presentations are considered bad prognostic factors [31]. There is an excellent rate of remission after appropriate chemotherapy. The remission rates are high at around 90% for 2 years which has been documented with the intensive chemotherapy regimen [39]. High intensity and short-duration chemotherapy, sometimes combined with the central nervous system prophylaxis, results in excellent survival in the pediatric age group. Pediatric patients with localized BL have a more than 90% 5-year survival rate [40]. The pediatric patients with extensive spread may achieve a more than 90% complete response rate, with an event-free survival rate at 4 years of approximately 65% in patients with leukemia presentation and 79% for those with stage IV BL reported in one series [41].

CONCLUSION

Primary Burkitt's lymphoma at the nasal cavity and nasopharynx in the pediatric age group is an uncommon clinical entity. Patients of primary BL in the nasal cavity and nasopharynx often present with insidious and non-specific clinical symptoms varying from nasal block to headache to hearing loss. The otolaryngologists and pediatricians must remain vigilant of this hemato-oncological

entity at the nasal cavity nasopharynx. BL in the pediatric age is usually aggressive but treatable. The definitive treatment is usually individualized as per the patient's age and tumor localization. BL is an aggressive neoplasm and is often considered a serious health condition, so prompt and appropriate treatment of the disease is always required.

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