Burkitt's lymphoma of the jaws: role of dental practitioner in management

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Abstract: *Burkitt s lymphoma, a malignant solid tumour of B lymphocytes grouped under the umbrella of non-Hodgkin s B-cell lymphoma. Burkitt s lymphoma is known to be endemic in Africa but can occur sporadically in other part of the world. It is one of the most aggressive malignancies in human body. In the past, the prognosis was very poor, however, complex chemotherapeutic regimens can now cure approximately 50-80 percent of adult patients with Burkitt s lymphoma, and in paediatric populations, the cure rate is even higher. This report describes a typical case of Burkitt s lymphoma of the jaws with associated rapid spread. This type of rapid progression calls for the need for prompt recognition and life saving referral by the general dental practitioner. The clinical features of Burkitt s lymphoma involving the jaws include severely mobile teeth, displaced teeth and generalized lymphadenopathy (submandibular, cervical, axillary and inguinal). The objective of this case report and review of the literature is to highlight the clinical and histopathological features of Burkitt s lymphoma to help general dental practitioner and clinicians recognize such cases readily and facilitate prompt and potentially life-saving referral.*

Key words: *Oncogenes, lymphoma, endemic, lymphadenopathy, chemosensitive (PHD 2004 Vol 11 No 1 Pages 89 - 93)*

Case presentation

A 5-year old Fijian boy presented with a two week history of facial swelling following tooth extraction in a health centre. The swelling occurred three days after the extraction of a grossly carious tooth. There was associated fever and anorexia but no vomiting. Patient was reviewed by a paediatrician at Colonial War Memorial Hospital and was admitted to paediatric intensive care unit (PICU).

Clinical examination revealed a boy who was afebrile, not pale with bilateral periorbital swelling and proptosis. Glasgow coma scale was 15/15. There were left discrete cervical and submandibular lymphadenopathy. Nodes were also palpable in the axillae and groins. Vital signs were within normal range and oxygen saturation was 97%. Intra oral examination revealed many carious teeth, gingival swelling and missing left molar (fig 1). The tonsils were covered with purulent exudates. Respiratory system findings were within normal limits. Non-tender hepatosplenomegaly was found in the abdomen. A clinical diagnosis of tonsillitis with sepsis was made and to exclude acute glomerulonephritis. Blood samples were obtained for serum creatinine, electrolyte and urea, liver function tests, serology (Anti-steptolysin "O" (ASO) titre), cerebrospinal fluid (CSF) and blood cultures. Throat swab was also taken. The patient was commenced on intravenous frusemide, crystalline penicillin, gentamicin, cloxacillin and later ceftriaxone. Oral paracetamol, chloramphenicol eye drops and ointment were also administered. He was also referred to Ear, Nose and Throat surgeon, ophthalmologist, orthopaedic and dental surgeons for review.

Clinically patient remained stable and responded to initial conservative management. However, the swelling persisted. Results of serum electrolyte, creatinine and full blood count were within reference range except for mild leucocytosis. There was a mild elevation in liver enzymes. Anti-steptolysin "O" (ASO) titre was 1:1280, blood and Cerebrospinal fluid cultures yielded no growth.

A review of X-rays of the facial bones revealed normal findings. Computed tomography of the head showed exophthalmos, bilateral post-septal enhancement and bilateral soft tissue swellings in the facial region. The swellings measured 3cm x 2cm (right side) and 1cm x 2cm (left side). There was no bony destruction. Facial orthopantomogram and abdominal ultrasound showed normal findings.

The patient had excision biopsy of submandibular lymph node on the eighth day of admission and a diagnosis of burkitt's lymphoma stage IV was made. Patient was discharged home with the swelling three weeks after admission with an explanation of the "anticipated poor" prognosis to the parents.

Literature review

Burkitt's lymphoma, a non-Hodgkin lymphoma, grows rapidly and requires early diagnosis and prompt referral by the general dental practitioner as well as early institution of specialized therapy. Non-Hodgkin's lymphomas of childhood and adolescence are a heterogeneous group of disease that constitutes 7-10 percent of all paediatric malignancies [1]. Although, Burkitt's lymphoma is chemosensitive and has a good prognosis when patients present early, early diagnosis and prompt referral by the general dental practitioner is the gold standard [2,3]. Hence the objective of this paper is to highlight the role of general dental practitioner in

the management of patients with Burkitt's lymphoma.

Epidemiology

Burkitt's lymphoma, a malignant solid tumour of B lymphocytes is endemic in some parts of Africa and sporadic in other areas. Perenial and intense malaria transmission (holoendemic malaria) and Epstein Barr virus (EBV) are two cofactors in the pathogenesis of endemic Burkitt's lymphoma [4-7]. Epstein Barr virus (EBV) is prevalent in all human populations and high titre of antibody correlate with Burkitt's lymphoma, Nasopharyngeal carcinoma and Hodgkin's disease.

In endemic areas, tumour cells in virtually all patients carry the EBV genome[4-6, 8]. EBV exhibits strong tropism for B cells and infects many B cells causing them to proliferate. In immunologically normal individuals, EBV-driven polyclonal B cell proliferation in vivo is readily controlled, and the individual either remains asymptomatic or develops a self-limited episode of infectious mononucleosis. In regions of the world where Burkitt's lymphoma is endemic, concomitant (endemic) malaria[4-6] impairs immune competence, allowing sustained B-cell proliferation. The activation of c-myc oncogenes causes further loss of growth control and the stage is set for additional gene damage which ultimately leads to the emergence of a monoclonal neoplasm. Histologically, the African and non-endemic Burkitt's lymphomas are identical, although there are clinical and virological differences[7]. In nonendemic areas [7] 80% of tumours do not harbour the EBV genome, but all tumours possess the specific translocation. This suggests that B-cells triggered by other mechanisms may also suffer similar mutations and give rise to non-African Burkitt's lymphoma[7].

Chromosomal translocation in Burkitt's lymphoma results in juxtaposition of the c-myc containing segment of chromosome 8 to chromosome 14q band 32

Pathogenesis and histopathologic findings:

Burkitt's lymphomas are tumours of B cells that express surface IgM and pan-B-cell markers such as CD 10, CD 19 and CD 20 antigen [7, 9]. Translocation-induced over expression of a protooncogene is exemplified in Burkitt's lymphoma. Tumour carry one of three translocations each involving chromosome 8q 24, where the c-myc has been mapped. Chromosomal translocation in Burkitt's lymphoma results in juxtaposition of the c-myc containing segment of chromosome 8 to chromosome 14q band 32. This places c-myc close to the immunoglobulin heavy chain (cμ) gene, a region with hectic transcriptional activity. Detached from its normal regulatory elements, the c-myc gene responds to relentless stimulation by its excitable and evidently seductive neighbour, and hence its product is expressed at a high level. In addition, the B-cells do not express cell surface antigens that can be recognized by host T-cells. Relieved from immunoregulation, such B-cells are at increased risk of acquiring mutations such as the [8, 14] translocation which activates the myc oncogene. This is a consistent feature in Burkitt's lymphoma [7].

Tumour cells are monotonous small lymphocytes with round or oval nuclei. The cytoplasm is usually faintly basophilic or amphophilic and often contains small lipid-filled vacuoles. A high mitotic rate is very characteristic of this tumour as is cell death accounting for the presence of numerous tissue macrophages with ingested nuclear debris. These macrophages are often surrounded by a clear space hence creating a "starry sky" appearance [7]. Burkitt's lymphoma has been classified into stages I, II, III and IV according to Murphy classification [10].

Clinical features

Both the endemic and non-African cases mainly affect children and young adults with age range 8months to 18years with male preponderance[7, 10-12]. Accounting for approximately 30% and 45% of childhood non-Hodgkin's lymphomas in the United States [7] and Kuwait [11] respectively. In both forms the disease rarely arises in lymph nodes. African Burkitt's lymphoma usually affects maxilla and mandible presenting as jaw swelling, mobile teeth, presence of palpable and multiple discrete non-tender submandibular, cervical, axillary and inguinal lymph nodes, failure of extraction socket to heal mimicking post extraction wound infection and post-extraction gingival swelling. Extraction of one of the mobile teeth usually leads to acceleration of tumour growth. Non-endemic Burkitt's lymphoma occurs in the abdomen (bowel, retroperitoneum, ovaries etc) [7, 11].

Treatment and prognosis

Intensive and sequential multiagent regimens or protocols such as COMP protocol [13], CEOP regimen [14], CHOP regimen [15], LMB-89 PROTOCOL [10, 12], COP/COMP [16]. French LMB regimen 17 to mention a few have all been found to be effective in children, but results are more variable in adults. Magrath et al has described a regimen that was found to be highly effective in children and as well as young adults [18].

In the past, the results of the treatment of non-Hodgkin in children have been poor due to inadequate chemotherapy and poor supportive care especially in developing countries. Currently, combination of systemic and intrathecal chemotherapy have resulted in better prognosis as supported by series of studies especially in children. Survival rates of 85% to 100% were being achieved with intensive short duration

protocols [3, 19]. The study carried out in National Cancer Institute, Bethesda, USA [3] reported the update results of an intensive treatment protocol for children (< 18years) and adults (> or = 18years) with advanced B-cell lymphomas. The protocol consists of two chemotherapy regimens: Regimen A, consisting of cyclophosphamide, doxorubicin, vincristine and high-dose methotrexate (CODOX-M) and Regimen B, consisting of ifosfamide, etoposide and a high-dose of cytarabine (IVAC). Both cycles included intrathecal chemotherapy (cytarabine or methotrexate). A total of four cycles is administered in the following sequence: A, B, A, B. Improved outcome was recorded both in children and adult and event-free survival rate of 85% at 1year was recorded. In older adults with Burkitt's lymphoma, the modified Magrath regimen was found to be effective and well tolerated [18].

Tumor lysis syndrome [20] (TLS) describes the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy. TLS results from the rapid destruction of malignant cells and massive release of intracellular ions, nucleic acids, proteins and their metabolites into the extracellular space. These metabolites can overwhelm the body's normal homeostatic mechanisms and cause hyperuriceamia, hyperkalaemia, hyperphosphatemia, hypocalcaemia and uraemia. TLS can lead to acute renal failure. Early recognition of patients at risk and initiation of therapy for TLS is essential. There is a high incidence of TLS in tumours with high proliferative rates and tumour burden such as Burkitt's lymphoma and acute lymphoblastic leukaemia. The mainstays of TLS prophylaxis and treatment include aggressive hydration and diuresis, Control of hyperuricaemia with allopurinol prophylaxis and vigilant monitoring of serum electrolyte.

There are myriads of causes of cervical lymphadenopathy but the important ones are reactive hyperplasia, infectious agents and malignancy.

Discussion

Burkitt's lymphoma usually first appears in the jaw (60 percent) [21] and patients will normally present to the general dental practitioner as it is in the case presented hence the diagnostic skills of general dental practitioners need to be polished .

Male gender and age as in the case presented are consistent with findings in Burkitt lymphoma.[3-5, 8, 10-13, 16] History of rapid facial swelling following extraction of a carious tooth with fever supported sepsis of dental origin. Bilateral periorbital swelling, proptosis, discrete cervical, submandibular, axillary and inguinal lymphadenopathy in an afebrile patient with normal vital signs suggested the presence of a malignant lesion.

Cervical lymphadenopathy is an important clinical sign which is very common in children especially in developing populations. There are myriads of causes of cervical lymphadenopathy but the important ones are reactive hyperplasia, infectious agents and malignancy. The lymph nodes are usually abnormal in size often more than 2cm in diameter, usually located in posterior triangle or supraclavicular fossa and may be generalized. Lymph nodes are hard, irregular and persist for more than 4-6weeks despite adequate antibiotic therapy. In children from developing countries, tuberculosis and Burkitt's lymphoma have to be kept in mind and diagnosis confirmed by excisional biopsy of the node just as in the case presented.

Non-tender hepatosplenomegaly suggested a reticuloendothelial lesion other than sepsis, though the presence of purulent tonsillar exudates further confuses the picture. The body fluid samples were correctly obtained before antibiotic therapy commenced. The results of investigation performed did not suggest sepsis though there was a mild leucocytosis but there was no differential count.

However, the excision biopsy of the nodes clinched the diagnosis of Burkitt's lymphoma.

In view of the current knowledge of new chemotherapeutic protocols available for Burkitt's (Small noncleaved) lymphoma is associated with high proliferative rates and tumour burden. However, over the past fifteen years, significant progress has been made in the understanding of the molecular mechanism involved in malignant transformation of lymphocytes as well as in the management and treatment of non-Hodgkin's lymphoma in childhood. This results in dramatic improvement in prognosis of children with Burkitt's lymphoma as indicated by series of studies world wide [10, 12-18]. The introduction of LMB-86 regimen significantly improved the disease –free survival of patients with advanced stages III and IV diseases; the prognosis of stages I-II and stages III-IV (without bone marrow involvement) in children with Burkitt's lymphoma is excellent [1, 22]. The patient presented would have done well if he was exposed to this novel treatment. Prognosis of Burkitt's lymphoma, even stage IV in a child is encouraging when treated appropriately.

Despite the efficacy of nowadays protocols, difficulty in management of malignant diseases is observed in developing countries as illustrated in the case presented due to factors such as diagnostic delay, late presentation of patients and high cost of chemotherapy. Although remarkable success have been observed in the treatment of the disease especially in paediatric patients,

complete remission is still very difficult to achieve in adults patients with the current chemotherapeutic protocol [10, 13-18]. The high cure rate obtained in most paediatric Burkitt's lymphoma allows an optimistic vision of future treatment

Conclusion

Burkitt's lymphoma is a high-grade tumour that has been suggested to be the fastest growing human neoplasm, however with aggressive modern chemotherapy, a long-term survival rate of 50% can be expected.

Burkitt's lymphoma responds well to chemotherapy and should not pose a significant threat to health, but sadly due to diagnostic delay, late presentation in some cases, and socioeconomic constraints, access to care for affected children has been denied; this readily treatable condition has become a cause of considerable distress and premature death in affected children as illustrated in the case presented.

There is need for the establishment and constant upgrading of national guidelines for management on agreed and achievable protocols.

Prognosis of Burkitt's lymphoma is directly related to the histopathologic staging at presentation. Best prognosis is achieved with Burkitt's lymphoma stage I and this may have a bearing on the diagnostic skills of the general dental practitioner who is usually the first contact with the patients in most cases. To address the challenge posed by diagnostic delay, this paper calls for the establishment of a policy in the dental act making Continue Medical Education compulsory for all practicing general dental practitioners and other oral health care providers in Fiji.

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Science may be described as the art of systematic over simplification
(Karl Popper August 1982)