Non Hodgkin’s Lymphoma of Buccal Mucosa Associated with AIDS - A Rare Case Report and Review of Literature

Dr. Manjula Kerketta¹ (MD), Dr. Suresh Kumar Thakur¹ (MD), Dr. Vikram Bali Rathore¹ (PhD), Dr. Vivek Choudhary² (MD), Dr. Surendra Kumar Azad³ (MD), Dr. Pradeep Kumar Chandrakar¹ (MD), Dr Rajeev Ratan Jain¹ (MD) and Dr Chandrahans Dhruv¹ (MD)

¹Assistant Professor, Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Medical College, Raipur, Chhattisgarh, India.
²Professor and Head, Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Medical College, Raipur, Chhattisgarh, India.
³Professor, Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Medical College, Raipur, Chhattisgarh, India.

Abstract: Primary Non hodgkin’s lymphoma (NHL) usually arises within the Lymphnode, but 20-30% accounts for extranodal sites. Buccal mucosa as a primary extranodal sites for non Hodgkins Lymphoma is relatively rare and represent 2.5% of all malignant lymphoma. HIV associated NHL are Extranodal and have a predilection for sites in the Head and Neck region in about 50-60% of cases. Of all the extranodal NHLs, oral constitutes only 25%. It is now considered that oral NHL serves as the first indicator of HIV infection. In this study, we present a case of Non Hodgkins Lymphoma of Right Buccal mucosa associated with AIDS and Review of literatures associated with it.

Keywords: Acquired Immuno Deficiency Syndrome, Buccal Mucosa, HAART, Non Hodgkin’s Lymphoma.

I. INTRODUCTION

Lymphomas are the heterogeneous group of malignancies that arise in lymphocytic progenitor cells. The association between HIV and lymphoproliferative malignancy is a well documented phenomenon. Approximately 3% of HIV positive patient will develop a lymphoma in the course of the disease. Non Hodgkins Lymphomas are 60 times more common in HIV/AIDS than in the general population (1, 2). The head and neck is the second most common region for extranodal lymphoma after gastrointestinal tract. Nevertheless, primary buccal mucosa is almost rare and really uncommon representing 2.5% of malignant lymphoma (3-9). Since 1981 and the emergence of the HIV pandemic, a close association between HIV infection and the development of a selected group of cancer has been noted. These malignancies include Kaposi sarcoma, high grade B cell non Hodgkin’s lymphoma, anal cancer and invasive cervical cancer (10). Certain Viruses such as the Epstein Barr virus (EBV), which normally causes glandular fever, might contribute to the development of lymphomas in particular Burkitt’s lymphoma, a high grade of B cell malignancy. EBV favors the rate of this lymphoma because it has the potential to transform normal human cell to immortalized cells. It is present in about 50% of Hodgkin’s and with varying frequency in non Hodgkin’s lymphoma (11, 12). High Grade B cell Non Hodgkin’s lymphoma (NHL) has been classified as an AIDS defining illness since 1985 following the description of NHL in 90 HIV seropositive men (13). The widespread introduction of Highly Active Anteretroviral therapy (HAART), since 1996 has led to dramatic reductions in AIDS related morbidity and mortality throughout the developed world (14, 15). This is largely due to the marked fall in incidence of the major opportunistic infections such as Pneumocystis carinii pneumonia (PCP), Cytomegalovirus (CMV), and Mycobacterium complex (MAC) (16).

II. CASE REPORT

A 36 Year old non smoker, non tobacco, occasionally alcohol addicted young man presented with the history of a slowly growing swelling over his right buccal mucosa of 4-months. The swelling was resistant to Non Steroidal Anti Inflammatory drugs (NSAIDs) and antibiotic therapy. It caused difficulty in opening his mouth in the past two months. During this period the patient also observed weight loss, fever, night sweat and weakness. The local examination revealed a firm to hard ulceroproliferative growth on the right side of buccal mucosa reaching up to the lower alveolus. The overlying skin was tense and shining. The mass was well circumscribed and appeared to be free from the bone. There was no lymph node enlargement. His blood investigation showed that the CBC was within normal limit with an increment of WBC (10.25 x 10³/ml) and
neutrophils 87.5% accompanied by lymphopenia. Clinical examination was confirmed with CT Scan which shows the presence of a hypervascularized mass of 7.1 x 2.6 cm² diameter in his right buccal mucosa with the absence of any cervical or submandibular lymph node. Biopsy was performed in order to obtain the histopathological typing that revealed a small diffuse B Cell Non Hodgkin Lymphoma. The immunophenotyping showed B cell type CD 10+ve, CD 45 +ve, CD 79A+ve, CD 67+ve, Ki 67+ve 95% . CD 138 focal +ve, and CD 3-ve, CD 20-ve, MIC-ve, CD 43-ve. He was advised for 6 cycle of chemotherapy CHOP regimen. Injection Cyclophosphamide 750 mg/m² I.V. on day 1, Injection Adriamycin 50mg/m² I.V. on day 1, Injection Vincristine 1.4mg/m² I.V. on day 1, Tablet Prednisolone 100 mg/m² orally day 1 to 5, along with highly active antiretroviral (HAART) therapy for AIDS. The patient responded well. Fig 1 and fig.2 shows the regression of disease prior and post chemotherapy respectively. There was complete disappearance of the growth. In last two cycles of chemotherapy he required blood transfusion. He was advised for monthly follow up with continuation of HAART but after two month of follow up to us, the patient absconded and did not turn up for follow up.

III. REVIEW OF LITERATURE

3.1 Epidemiology
The Burden of HIV/ AIDS in India is large with almost 3.5 million persons infected as estimated by UNAIDS Reports on the Global Epidemic 2013. General issues is that Twenty-five to 40 percent of human immunodeficiency virus (HIV)-positive patients will develop a malignancy, with approximately 10 percent developing non-Hodgkin lymphoma (NHL). These lymphomas appear to be more common in males than in females, regardless of antiretroviral use.

3.2 Histopathology
The classification of NHL aims to help the pathologist to recognize the diagnosis, the clinician to treat the patient, and the scientist to unravel the biology of the tumor. Initial classifications, such as the Rappaport Classification, were based upon the morphological appearance of formalin fixed haematoxylin and eosin stained tumors. Subsequent classifications have incorporated the use of immunophenotyping of cluster designation (CD) antigens, cyogenetics and molecular analysis. The latest classification of NHL is the revised European and American Lymphoma Classification (REAL) .Within this classification approximately two third of all AIDS related NHL are diffuse large cell lymphomas which includes all immunoblastic lymphoma while one third are small non cleaved cell lymphoma (which includes Burkitts lymphoma) (17-22). Primary effusion lymphoma (PEL) or body cavity based lymphoma (BCBL) is a rare variant of HIV associated lymphoma that is characterized by effusions in serosal cavities, (pleura, pericardium and peritoneum) in the absence of solid nodal masses (23).

3.3 Pathogenesis
It is thought that immune stimulation by HIV virus (24) and reactivation of previous EBV infection due to defective T cell surveillance, leads to long term stimulation and proliferation of B lymphocytes resulting in the development of AIDS related NHL. Moreover, even in the absence of EBV infection, HIV induces the production of inflammatory cytokines that cause B cell stimulation, proliferation and activation (25-27). Cell lines derived from AIDS related NHL have been found to express cytokines including interleukin 6, interleukin 10, and tumour necrosis factor B (28). In addition of EBV and c-Myc other genetic events have been identified in AIDS related NHL that may contribute to the pathogenesis of these tumors. The tumor suppressor gene p53 has a central role in cell cycle control and hence regulates cell replication. About 40% of HIV associated NHL have been found to have mutations of p53 gene. These mutations are found most commonly associated with the small non cleaved cell or Burkitt like variants rather than the diffuse large cell histologies (29-31). The role of HIV itself in the development of NHL appears to be confined to its lymphoproliferative effect; indeed one tumor has been described that secreted a monoclonal paraprotein directed at group 160 antigen of HIV (32-33).

3.4 Clinical Features
Patients with HIV associated NHL more frequently present with advanced disease and/or extranodal disease than immuno competent patients and B symptoms occur in upto 90% of patients (34, 35). The commonest site of extranodal disease is the gastrointestinal tract (36), particularly the small intestine, stomach and perianal region. Similarly, hepatic involvement occurs in upto one quarter of patients and results have suggested that the prognosis is poor (37). Bone Marrow involvement by lymphoma occurs in upto 20% (38) although trilineage myelodysplasia is almost ubiquitous owing to the HIV and may add to the myelotoxicity of cytotoxic chemotherapy treatments. In addition to primary cerebral lymphoma central nervous system involvement by systemic NHL is frequent. Leptomeningeal disease may be present at diagnosis and is asymptomatic in upto 20% patients with AIDS related systemic NHL (39), this is why all the patients should
have a diagnostic staging lumbar puncture. In addition, the cerebrospinal fluid is a common site of relapse and prophylactic intrathecal chemotherapy should be administered to patients.

3.5 Treatment
The optimal treatment modality for AIDS associated NHL is the combination chemotherapy, as patients usually have disseminated disease and extranodal involvement at presentation (40). Patients with the major adverse prognostic factor as (Low CD 4 cell counts, poor performance status and previous AIDS defining illness are treated with palliative intent using mild chemotherapy and/or radiotherapy. Upto 30-40% of patients with good prognostic features will remain in remission following treatment until another AIDS related illness ensues. Recent studies have reported higher median survival with no change in response rates for AIDS related NHL (41). It is speculated that this improvement is due to reduced incidence of opportunistic infections in the HAART era among patients who have durable remissions of their NHL. Sparano et al used the combination of cyclophosphamide doxorubicin and etoposide administration as a 96 hour continuous infusion for upto six courses at 4 weekly intervals together with granulocyte colony stimulating factor (G-CSF) and nucleoside reverse transcriptase inhibitors.

3.6 Haematopoietic Growth Factors
Patients in the good prognostic category may be treated with conventional NHL chemotherapy regimens with the aim of cure. However, because of the underlying immuno-deficiency, poor bone marrow reserve owing to HIV myelodysplasia, and concomitant use of myelosuppressive agents such as Zidovudine and Ganciclovir, many patients develop opportunistic infections, neutropenic sepsis or persisting neutropenia causing chemotherapy delays and hence suboptimal treatment. The use of bone marrow stimulatory factors may facilitate the use of chemotherapy but improved survival has not been demonstrated.

3.7 Anti Retroviral Drugs
The concomitant use of antiretroviral agents with chemotherapy in generally acceptable practice with the exception of Zidovudine, which significantly adds to the myelosuppression of combination chemotherapy and Didanosine, which may worsen the peripheral neuropathy caused by Vinca alkaloids. Little is known about the interactions of protease inhibitors and chemotherapy although the inhibition of p450 may reduce hepatic metabolism of cyclophosphamid and the anthracyclines. For these reasons the infusional schedule EPOCH (etoposide, predinsolone, vincristine cyclophosphamide and doxorubicin) has been developed at the National Cancer Institute and omits all antiretroviral therapy for the duration of chemotherapy. In addition to the impressive response rate reported, there has been a restoration of immune function as measured by CD4 cell count and HIV mRNA viral load within 3 months of the reintroduction of antiretroviral therapy after completing the chemotherapy (42).

3.8 Intrathecal Chemotherapy
There is a high rate of meningeal involvement in HIV associated systemic NHL and it is not necessarily associated with bone marrow involvement or a poor prognosis. Although the frequency of meningeal relapse can be reduced by the use of prophylactic intrathecal chemotherapy this necessitates repeated lumbar punctures. Intrathecal methotrexate or cytosine arabinoside should therefore be given to patients with meningeal disease or at high risk of cranial disease by virtue of Burkitts histology or extensive paranasal sinus and base of skull disease.

3.9 New Development
MGBG (Methyl glyoxal bis guanylhydrazone) is a relatively non-myelotoxic spermidine analogue which inhibits cellular polyamine synthesis and has been used with some success in both relapsed systemic NHL and in primary cerebral NHL. Further more studies of Rituximab, a humanized monoclonal antibody to CD 20 are underway in this group of patients.
Figure-1: Non Hodgkins lymphoma of Buccal Mucosa of an HIV positive patient prior to Chemotherapy.

Figure-2: Non-Hodgkins lymphoma of buccal mucosa after chemotherapy.
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REFERENCES


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