48 Monte Carlo Crescent
Kyalami Business Park
Kyalami, Johannesburg, 1684, RSA
Tel: +27 (0)11 463 3260
Fax: + 27 (0)86 557 2232
Email: ThistleQA@LGCgroup.com
www.thistle.co.za

Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: MT- 16/009

Each attendee should claim THREE CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 49 SLIDE 3

Burkitt Lymphoma

Burkitt Lymphoma also known as Burkitt's tumor, or malignant lymphoma Burkitt's type, is a cancer of the lymphatic system, particularly B lymphocytes found in the germinal center. It is named after Denis Parsons Burkitt, a surgeon who first described the disease in 1958 while working in equatorial Africa.

Classification

Currently Burkitt lymphoma can be divided into three main clinical variants: the endemic, the sporadic, and the immunodeficiency variants.

- The endemic variant also called African variant most commonly occurs in children living in malaria endemic regions of the world (Africa, Brazil, and Papua New Guinea). Epstein-Barr virus infection is found in nearly all patients. Chronic malaria is believed to reduce resistance to EBV, allowing it to take hold. The disease characteristically involves the jaw or other facial bone, distal ileum, cecum, ovaries, kidney or breast.

- The sporadic type of Burkitt lymphoma also known as non-African is the most common variantfound in places where malaria is not holoendemic. The tumor cells have a similar appearance to the cancer cells of classical endemic Burkitt lymphoma. Sporadic lymphomas are rarely associated with the Epstein-Barr virus. Non-Hodgkin lymphoma, which includes Burkitt's, accounts for 30-50 % of childhood lymphoma. The jaw is less commonly involved, compared to the endemic variant. The ileocecal region is the common site of involvement.

- Immunodeficiency associated Burkitt lymphoma is usually associated with HIV infection or occurs in the setting of post-transplant patients who are taking immunosuppressive drugs. Burkitt lymphoma can be one of the diseases associated with the initial manifestations of AIDS.

By morphology (microscopic appearance) or immunophenotype, it is almost impossible to differentiate these three clinical variants. Immunodeficiency-associated Burkitt lymphoma may demonstrate more plasmacytic appearance or more pleomorphism, but these features are not specific.

Diagnosis

- Malignant B cell characteristics: Normal B cells of a germinal center possess rearranged immunoglobulin heavy and light chain genes, and each isolated B cell possesses a unique IgH gene rearrangement. Since Burkitt lymphoma and other B cell lymphomas re a clonal proliferative process, all tumour cells from one

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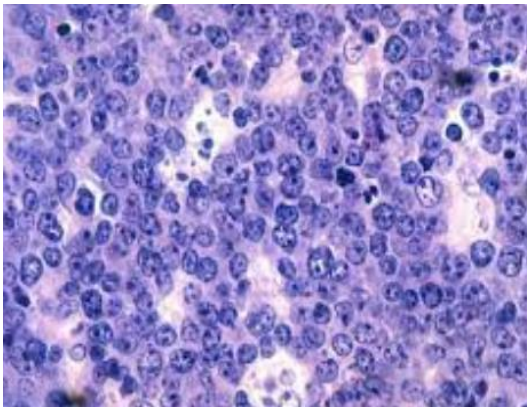
patient are supposed to possess identical IgH genes. When the DNA of tumour cells is analysed using electrophoresis, a clonal band can be demonstrated, since identical IgH genes will move to the same position. On the contrary, when a normal or reactive lymph node is analysed using the same technique, a smear rather than a distinct band will be seen. This technique is useful since sometimes benign reactive processes and malignant lymphoma can be difficult to distinguish.

- Microscopy: The tumour consists of sheets of a monotonous population of medium sized lymphoid cells with high proliferative activity and apoptotic activity. The "starry sky" appearance seen under low power is due to scattered tangible body-laden macrophages. The old descriptive term of "small non-cleaved cell" is misleading. The tumour cells are mostly medium in size. "Small non-cleaved cells" are compared to "large non-cleaved cells" of normal germinal centre lymphocytes. Tumour cells possess small amounts of basophilic cytoplasm with three to four small nucleoli. The cellular outline usually appears squared off.

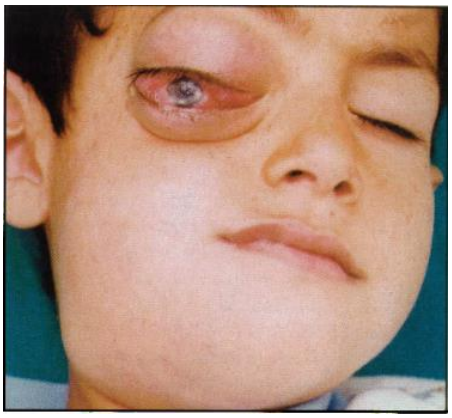
- Immunochemistry: The tumour cells in Burkitt lymphoma generally strongly express markers of B cell differentiation (CD20, CD22, CD19), as well as CD10 and BCL6. The tumour cells are generally negative for BCL2 and TdT. The high mitotic activity of Burkitt lymphoma is confirmed by nearly 100% of the cells staining positive for Ki67.

Pathophysiology

- Genetics: All types of Burkitt lymphoma are characterized by dysregulation of the c-myc gene by one of three chromosomal translocations. This gene is found at 8q24. The most common variant is t(8;14)(q24;q32), which accounts for about 85% of cases. This involves c-myc and IGH@. A variant of this, a three way translocation t(8;14;18), has also been identified. A rare variant is at t(2;8)(p12;q24). This involves IGK@ and c-myc. Another rare variant is t(8;22)(q24;q11). This involves IGL@ and c-myc. Combined the two less-common translocations t(2;8)(p12;q24) and t(8;22)(q24;q11), account for the remaining 15% of cases not due to the t(8;14)(q24;q32) translocation.
- Micro RNA expression: In 2014, it was described that short non-coding RNAs names microRNAs have important functions in lymphoma biology. In malignant B cells microRNAs participate in pathways fundamental to B cell development like B cell receptor signaling, B cell migration, cell-cell interactions in immune niches and the production and class-switching of immunoglobulins. MicroRNAs influence B cell maturation, generation of pre-marginal zone, follicular, B1, plasma and memory B cells.



"Starry sky" appearance of cells



Non-African Burkitt lymphoma manifesting at the Orbit and Jaw

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Treatment

Treatment may be dose-adjusted EPOCH with rituximab or the modified Magrath regimen (R-CODOX-M/IVAC). Other protocols are CHOMP COPADM, hyper-CVAD, an the Cancer and Leukemia Group B (CALGB) 8811 regimen, these can be associated with rituximab. The effects of the chemotherapy, as with all cancers depend on the time of diagnosis. With faster growing cancers such as Burkitt lymphoma, the cancer actually responds faster than with slower growing cancers. This rapid response to chemotherapy can be hazardous to the patient, as a phenomenon called "tumor lysis syndrome" could occur. Close monitoring of the patient and adequate hydration is essential during the process. Since Burkitt lymphoma has high propensity to spread to the Central nervous system, intrathecal chemotherapy with methotrexate, ARA-C and prednisolone is given alongside with systemic chemotherapy. Other treatments for Burkitt lymphoma include immunotherapy, bone marrow transplants, stem cell transplant, surgery to remove the tumor and radiotherapy.

Prognosis

Treatment with dose adjusted EPOCH with rituximab has shown an eight year survival rate of 91% for low risk, 90% for low-intermediate risk, 67% for high-intermediate risk and 31% for high risk cases with few of the side effects associated with Burkitt lymphoma chemtherapy.

Epidemiology

Of all cancers involving the same class of blood cell, 2.3% of cases are Burkitt lymphoma. Epstein Barr virus infection is strongly correlated with this cancer

Research

Gene Targets: Unique genetic alterations promote cell survival in Burkitt lymphoma, distinct from other types of lymphoma. These TCF3 and ID3 gene mutations in Burkitt correspond to a cell survival pathway that may be found to be amenable to targeted therapy.

References

1. http://em.wikipedia.org/w/index.php?title=Burkitt%27slymphoma&oldid=748386881

Questions

1. Name the three clinical variants that Burkitt lymphoma is divided into
2. What is the "starry sky" appearance due to during microscopy?
3. What infection is strongly correlated with Burkitt lymphoma?