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Case Report

Primary Burkitt-like lymphoma of the orbit diagnosed using ultrasound-guided core needle biopsy: A case study



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ABSTRACT

Burkitt-like lymphoma, also known as (B-Cell lymphoma, Unclassifiable) is a rare extra-nodal B-cell lymphoma with features intermediate between Burkitt's lymphoma and diffuse large B-cell lymphoma.

A 73-year-old Caucasian female presented to our Emergency Department with orbital pain, deterioration of vision, nausea and vomiting. General examination revealed right orbital proptosis and reduction in visual acuity; and computed tomography confirmed the presence of a right retro-bulbar mass.

Tissue samples were obtained using ultrasound-guided core needle biopsy. An experienced head and neck radiologist (SM) undertook the procedure under general anaesthesia, using a lateral orbital approach. The instrument used was the Toshiba Aplio. The procedure was without complication. Results from histopathological, immunohistochemical and genetic analyses confirmed the diagnosis of stage IV orbital Burkitt-like lymphoma with atypical features.

Despite the ambiguity of immunohistochemistry and cytogenetic results, the patient was treated for Burkitt's lymphoma. The treatment had to be re-adjusted after two rounds of chemotherapy as the patient developed chemotherapy-induced encephalopathy. The patient remained symptom-free for 8 months. This case demonstrates the application of ultrasound-guided core needle biopsy for rapid and accurate lymphoma diagnosis and sub-classification.

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1. Introduction

Primary non-Hodgkin's lymphoma (NHL) of the orbit is a rare presentation of extra-nodal lymphoma comprising just 1% of all NHL cases [1]. Of these, only 16% of cases show high-grade histology, with the rest being indolent. Of the various histological types, the majority of orbital lymphomas (57%) are mucosa associated lymphoid tissue (MALT) lymphomas. Others include follicular

lymphomas (19%), diffuse large B-cell lymphomas (DLBCL), and mantle cell lymphomas [2,3].

Burkitt's Lymphoma (BL) is a type of high-grade, extra-nodal B-cell lymphoma defined by morphological, immunohistochemical and genetic criteria. Myc oncogene rearrangements are universal to all three types of BL: endemic (eBL), immunodeficient (iBL) and sporadic (sBL) [4]. eBL affects children in tropical climates suffering from chronic malaria and Epstein-Barr Virus (EBV). iBL is associated with the acquired immunodeficiency syndrome (AIDS) and EBV superinfection. sBL, which represents approximately 1% of adult lymphomas, is not geo-specific and only 15–30% of cases are EBV sero-positive. Whilst orbital involvement is common to both eBL and iBL, it is a rare presentation in sBL.

Burkitt-like lymphoma (BLL) is a rare entity, and describes B-cell NHL with features intermediate between sBL and DLBCL. The different therapeutic regimens used to treat these pathologically distinct

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lymphomas highlight the difficulties faced when diagnosing and treating BLL [5].

Diagnosis of orbital tumours is complicated by challenging anatomy which includes the eye, optic nerve, peripheral nerves and vasculature confined to an approximate volume of 30 ml. Studies have demonstrated superior diagnostic accuracy achieved using core needle biopsy (CNB) as compared to fine needle aspiration (FNA) in assessing head and neck lesions [6,7].

Herein, we describe a case of Burkitt-like lymphoma involving the retro-bulbar region that was diagnosed using Ultrasound (US)-guided CNB (Core Needle Biopsy).

2. Case report

A 73-year-old Caucasian female with medical history of hypertension, epilepsy and peripheral neuropathy was admitted to the Emergency Department at University College Hospital, London, with orbital pain, deterioration of vision, nausea and vomiting. General examination of the head and neck revealed right proptosis, reduced visual acuity and impaired visual fields. There were no other focal neurological signs. Observation of the patient's vital signs revealed elevated blood pressure, heart and respiratory rates with 99% oxygen saturation on air. The patient remained apyrexial with a Glasgow Coma Scale (GCS) of 15/15.

Haematological investigations revealed increase in inflammatory markers, while biochemical investigations were within normal range. Virology screening was negative. A CT (computed tomography) of the head and neck was sought almost immediately and confirmed the presence of a right retro-bulbar mass (Fig. 1A). The initial working diagnosis included lymphoma, tumour metastasis, optic nerve glioma and meningioma.

To confirm the diagnosis, an ultrasound-guided 16-gauge core needle biopsy (CNB) was performed under general anaesthesia using a lateral orbital approach (Fig. 1B and C). The procedure was carried out by an experienced head and neck radiologist and two tissue samples, each measuring 3 mm in diameter, were obtained. The procedure was uncomplicated. Results from histological, immunohistochemical and genetic analyses of the two specimens are given in Table 1. Immunohistochemistry images are shown in Fig. 2.

Despite ambiguity of immunohistochemistry and cytogenetic results, the patient was treated for Burkitt's lymphoma with the R-CODOX-M regimen (Rituximab, Vincristine, Cyclophosphamide, Cytarabine, Doxorubicin and Methotrexate). The treatment was well tolerated by the patient and the initial results showed satisfactory resolution of the retro-bulbar mass and dissipation of marrow infiltrate. After two rounds of treatment, the patient developed a chemotherapy-induced encephalopathy and she was immediately placed on a less intensive regimen (R-CHOP with intrathecal cytarabine) of which she received 3 courses. The patient remained symptom-free for 8 months.

3. Discussion

Historically, invasive excisional biopsy was thought to be the gold standard in diagnosing head and neck lesions, allowing sufficient tissue volume and preserving tissue architecture. However, in cases of deep seated lesions, and complex anatomy such as in this case, excisional biopsies can cause significant morbidity to the patient due to the risk of bleeding, infection and damage to adjacent structures such as the optic nerve. Therefore, minimally invasive procedures such as fine needle aspirate (FNA) and core needle biopsy (CNB) which present less risk are preferred.



Fig. 1. (A) Computed tomography (CT) with contrast showing a retro-bulbar lesion of mass measured at 3 cm × 2.5 cm × 3 cm (white arrow) surrounding the optic nerve with proptosis of the right eye. (B) Clinical image showing the ultrasound-guided core needle biopsy procedure. (C) An ultrasound image of the procedure at time of acquiring the tissue samples. The white arrow is showing the tip of the needle while being inserted in the lesion.

Table 1
Selected histological, immunohistochemical and genetic features of diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL), Burkitt's-like lymphoma (BLL) and those obtained from the tumour described in this case report (present case).

| Features | DLBCL | BL | BLL | Present case |
|-------------------------------------|---|---|---|--|
| Histological Features | | | | |
| Cell size | Large | Medium | Medium | Medium/large |
| Nuclei | Round-Oval, Irregular | Round | Round-Oval, Irregular | Round |
| Nucleoli | Prominent | Prominent, multiple | Prominent, single | Prominent |
| Mitotic activity | Lower | Very high | Very high | Very high |
| Starry sky pattern | Less common | Nearly all | Yes | Yes |
| Derivation | Germinal Centre | Early Germinal Centre | Early Germinal Centre | ?? |
| Ki-67 proliferation index | <90% | >95% | <95% | 96% |
| Immunohistochemical features | | | | |
| B-cell | CD19+, CD20+ | CD19+, CD20+, CD22+, CD79a+, sIgM+ | CD19+, CD20+, CD22+, CD79a+ | CD20+, CD21-, sIgM+ |
| GC markers | CD10+/-, BCL6+/-, TCL1-, MUM1+, CD44+, CD138+/- | CD10+, BCL6+, TCL1+, MUM1-, CD44-, CD138- | CD10+/-, BCL6+/, MUM1- | CD10+, BCL2+, BCL6-, MUM1+, CD138- |
| Genetic features | | | | |
| Karyotypes | Complex | Simple | Complex | Complex, T(14;18)(q32;q21) T(X;4)(q13;q12) Del(13)(q12q14) Loss (16) Del(17)(p10) |
| Oncogenes | BCL2+ MYC-negative BCL6 rearrangement BCL2 rearrangement | BCL2- Ig-MYC rearrangement | BCL2+ Ig-MYC rearrangement Non-Ig-MYC rearrangement MYC+BCL2 rearrangement Variable | BCL2+ TP53 deletion |

Adapted from Thomas et al. [5].

Although FNA specimens permit flow cytometry, lack of tissue architecture has been shown to compromise accurate diagnosis in 71% of cases ($n=93$) [8]. For this reason, CNB, which preserves tissue architecture, represents the best compromise between minimally invasive approach and optimizing chances for full diagnosis and sub-classification. However, lack of tissue architecture due to small CNB is cited as a major impediment to hematopathological sub-classification of suspected lymphoma [9].

Here we demonstrate a safe and effective application of US-guided CNB to diagnose an unusual primary retro-bulbar lymphoma. Our case builds on a recent study showing effective use of orbital CNB, which demonstrated 88% ($n=50$) concordance between CNB and surgical diagnosis [10]. However, only 11 cases in the study were deep-seated, requiring ultrasound guidance. In our case, use of a 16 g needle yielding two 3 mm biopsies was sufficient for full histologic and immunohistochemical characterization enabling rapid diagnosis of lymphoma and sub-classification of possible Burkitt's lymphoma.

Other approaches, such as FNA or excisional biopsy, may have led to incomplete diagnosis delaying vital therapy or unnecessary morbidity. Although the high Ki-67 proliferation fraction together with morphological and immunohistological features suggested infiltration by Burkitt's lymphoma, only genetic tests on bone marrow trephine biopsies were able to clinch the diagnosis of Burkitt-like lymphoma [11]. On the other hand, it has been shown that flow cytometry can be successfully performed on CNB specimens of adequate size. Thus, CNB may represent a single diagnostic solution making it unnecessary for patient's to undergo additional painful procedures such as marrow trephine biopsies [9].

In addition, this case represents probably the first reported case of an unusual presentation of a rare B-cell lymphoma known as Burkitt-like lymphoma of the orbit.

The immunogenetic features of this case are also unique. A recent study reports median overall survival for BLL of approximately 330 days [12]. In comparison our patient's overall survival at 240 days was 27% below the median. Surprisingly,

only one translocation (IGH/BCL2) was found in this lymphoma. Consequently, so-called 'double-hit' lymphomas containing two rearrangements typically associated with a poor prognosis does not explain this patient's shorter than expected survival. As shown in Table 1, this neoplasm shared many immunogenetic features with DLBCL and BL, and was not entirely in keeping with those features considered to be typical of BLL in the literature. Of note, the tumour had histologic features closely resembling those considered typical of BL, especially the proliferation index (96%).

However, it was genetically dissimilar to BL as it did not contain any MYC rearrangements and was BCL2-. High Ki-67 has previously been considered as a surrogate for MYC rearrangements, this case is therefore a further example against using Ki-67 for this purpose [5]. TP53 loss, in conjunction with the complex translocations and chromosomal deletions detected, is likely to have contributed to this patient's rapid clinical progression. TP53 loss is associated with 17p deletions, and has previously been correlated with poor survival in DLBCL. [13] This is probably because c-MYC and p53 are co-dependent with the proliferative effect of C-MYC being counteracted by tp53-mediated activation of pro-apoptotic targets including NOXA, PUMA and BAX [14].

Paradoxically, this case showed the infiltrate cells are MUM1 positive (marker of germinal centre and post-germinal centre B-cells) but BCL-6 negative (marker of germinal centre B-cells) and CD138 negative (marker of post-germinal centre B-cells) indicating lymphoid cell differentiation may have occurred. Burkitt's lymphoma and a large proportion of DLBCL are known to derive from B-cells residing in the germinal matrix [15]. BLL has typically been thought to derive from the early germinal centre (dark zone) [5]. However MUM1 expression is typically seen in the light zone, and therefore this case suggests that BLL transformation may also occur in the late germinal centre (light zone). Finally, absence of BCL-6 and CD138 expression in this case suggests that MUM1 may be a more sensitive marker for histogenetic characterization of the BLL subtype.

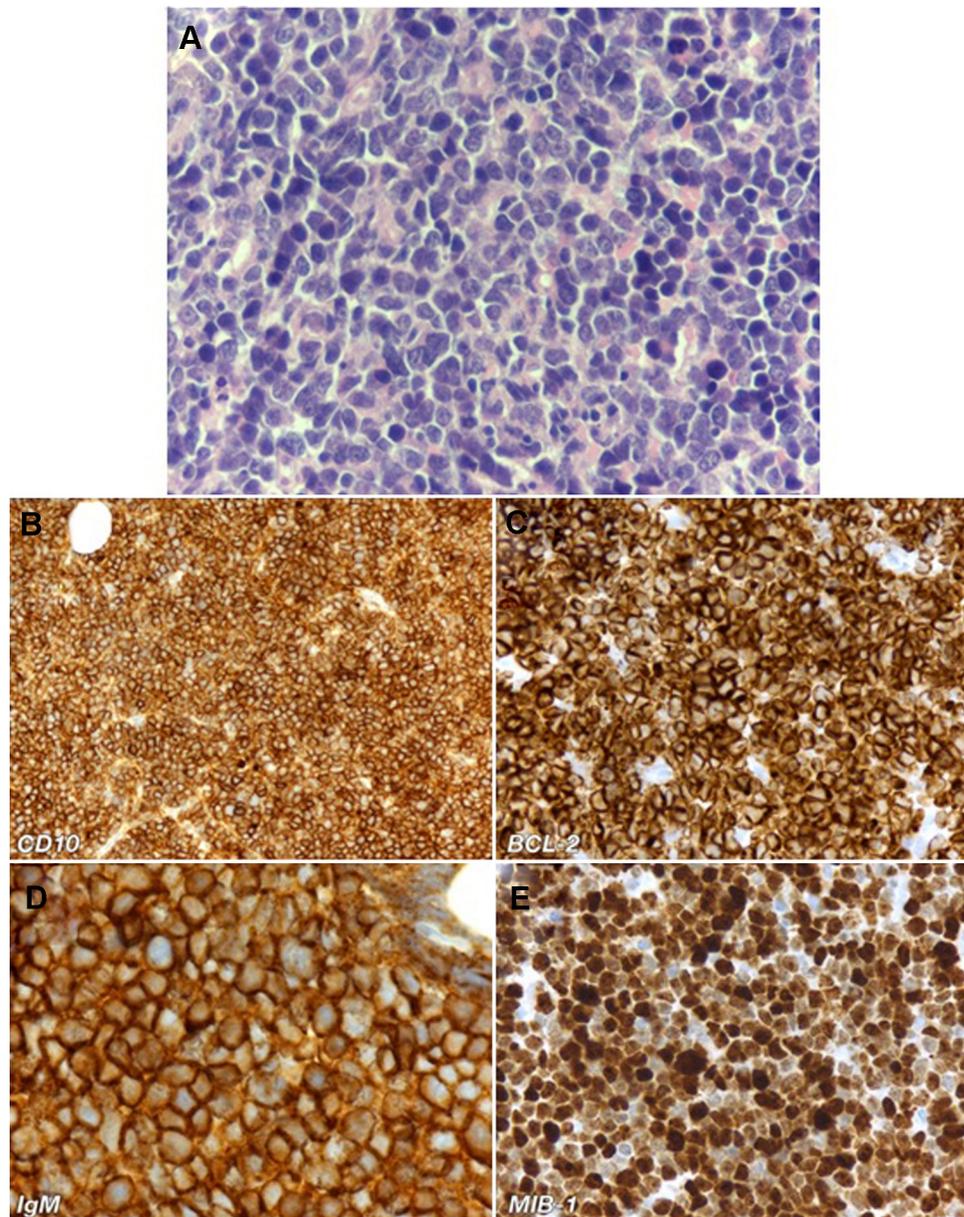


Fig. 2. (A) H & E stained section with a high grade B cell neoplasm (magnification: 60×), (B) (magnification: 10×), (C) (magnification: 40×), (D) (magnification: 60×), (E) (magnification: 40×): Selected immunohistochemistry stains demonstrating features of Burkitt-like lymphoma.

4. Conclusion

This case study shows that ultrasound-guided core needle biopsy which is a minimally invasive technique provides a rapid and more accurate way of obtaining biopsies from the retro-bulbar area and should supersede the use of an FNA biopsy as an alternative diagnostic tool.

Since both prognosis and treatment are based on lymphomas and their subclasses, correct diagnosis and classification of B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma is important, thus the need for more efficient minimally invasive diagnostic tool such as ultrasound-guided core needle biopsy is important.

In addition, we have presented an unusual case of MUM1+, BCL6– and CD138– Burkitt-like lymphoma with an unusual karyotype. Considering recent publications about MUM1 as a marker of advanced B-cell differentiation, this case suggests that in some

instances, BLL may derive from late germinal centre B-cells and not early germinal centre B-cells as is generally accepted in the literature.

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