

## Case report

## Isolated orbital mass as the primary presentation of a triple-hit lymphoma transformed from a systemic follicular lymphoma

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## ABSTRACT

**Purpose:** Triple-hit lymphoma is a highly aggressive B-cell lymphoma. We report a case of triple-hit lymphoma transformed from systemic follicular lymphoma (FL) after 9-year remission and presented primarily as an isolated orbital mass without systemic symptoms or lymphadenopathy.

**Observations:** A 58-year-old female presented with intermittent vertical binocular diplopia, left upper eyelid swelling and pain and was found to have a 2.9 cm orbital mass. Histological section revealed a CD10-positive large B-cell lymphoma, consistent with transformation of FL. Fluorescent *in situ* hybridization (FISH) analysis demonstrated rearrangements involving *C-MYC*, *BCL-2* and *BCL-6* genes, indicating a high grade, triple-hit lymphoma.

**Conclusions and importance:** Triple-hit lymphoma transformed from a low-grade lymphoma may initially present as an isolated orbital mass without systemic evidence of transformation. Early recognition of double or triple-hit lymphomas is important since these patients require aggressive chemotherapy.

## 1. Introduction

Diffuse large B-cell lymphoma (DLBCL) can occur *de novo* or as a transformation from low-grade lymphomas, most frequently follicular lymphoma (FL).<sup>1,2</sup> FL typically harbors *BCL-2* rearrangement; acquisition of *C-MYC* rearrangement during transformation occurs in about 20% of patients (double-hit lymphoma).<sup>2</sup> Rarely, *BCL-6* rearrangement is seen together with *BCL-2* and *C-MYC* (triple-hit lymphoma). Double or triple-hit lymphoma used to be classified as “B-cell lymphoma, unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BL)” due to its unique morphologic, phenotypic and genetic features overlapping DLBCL and BL. They are now classified as “high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement” based on the 2016 WHO classification.<sup>3</sup> Double- or triple-hit lymphomas are highly aggressive and require intensive chemotherapy.<sup>4</sup> Here we report an unusual case in which an isolated orbital mass was the primary presentation of a triple-hit lymphoma transformed from a systemic FL after 9-year remission.

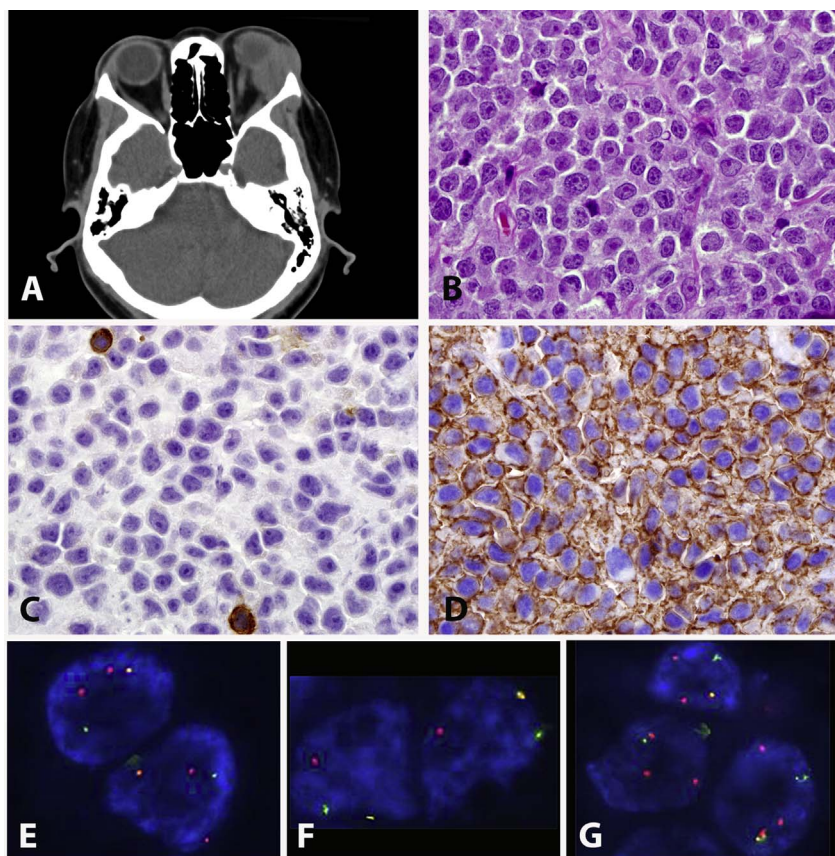
## 1.1. Case report

A 58-year-old female presented with complaints of left upper eyelid

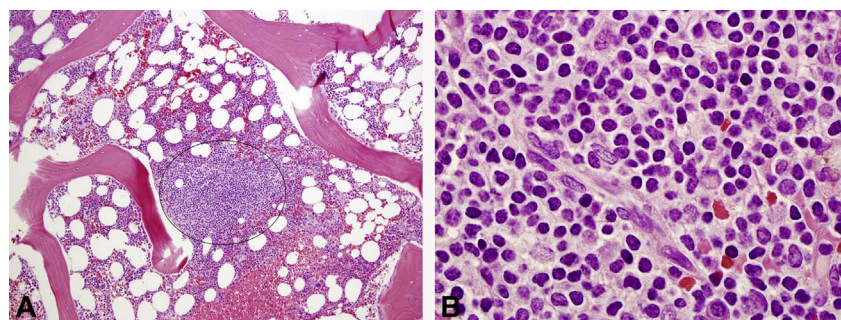
swelling, aching around the left eye and intermittent vertical binocular diplopia for 6 weeks. She denied change in visual acuity, fever, weight loss and night sweats. On examination, the patient had proptosis with downward displacement of the globe, and a non-tender mass in the area of the left lacrimal gland. CT scan revealed a well-circumscribed 2.9 × 1.9 × 2.9 cm mass in the extraconal soft tissue involving the lacrimal gland (Fig. 1A). She had a history of FL diagnosed 9 years ago on a cervical lymph node biopsy and had been in remission after treatment with eight cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Given this history, the orbital mass was clinically thought to be possible relapsed FL. Other differential diagnosis included epithelial neoplasm, idiopathic orbital inflammatory disease and other specific inflammatory diseases.

A biopsy of the orbital mass revealed diffuse infiltration of medium to large lymphocytes with prominent nucleoli (Fig. 1B), and these cells were negative for CD3 and positive for CD20 (Fig. 1C and D) and CD10 (not shown), consistent with DLBCL transformed from FL. FISH analysis revealed rearrangements involving *C-MYC*, *BCL-2* and *BCL-6* genes in over 90% of cells (Fig. 1E, F, G), indicating a triple-hit lymphoma. The subsequent work-up demonstrated slightly elevated LDH, small foci of uptake in lymph nodes, and < 5% bone marrow involvement by a low-grade FL (Fig. 2).

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**Fig. 1.** Computed Tomography (CT) scan, histology, immunohistochemistry and fluorescent *in situ* hybridization (FISH) analysis of the orbital mass. (A) CT scan showed a  $2.9 \times 1.9 \times 2.9$  cm mass in the left extraconal soft tissue involving the lacrimal gland. (B) The biopsy shows diffuse proliferation of large lymphoid cells with prominent nucleoli. (C) The large cells are negative for CD3. (D) The large cells are positive for CD20. FISH analysis using break-apart probes from Abbott was positive for (E) *C-MYC* (unbalanced), (F) *BCL-2*, and (G) *BCL-6* (unbalanced) gene rearrangements. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04113.



**Fig. 2.** Bone marrow biopsy. (A) Low power view of bone marrow biopsy showing a small to medium sized lymphoid aggregate. (B) High power view showing the lymphoid aggregate is composed of small lymphocytes. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04114.

The patient was treated with one cycle of R-ICE (rituximab, ifosfamide, carboplatin and etoposide), but switched to R-GD (rituximab, gemcitabine and decadron) due to toxicity. She went into remission and was on maintenance rituximab for two years. Unfortunately, she died of cardiac failure three years later.

## 2. Discussion

Double- and triple-hit lymphomas are high-grade B-cell lymphomas harboring *MYC* rearrangement and *BCL2* and/or *BCL6* rearrangements.<sup>3</sup> These lymphomas often show morphologic features overlapping between DLBCL and BL.<sup>3</sup> They are highly aggressive and refractory to chemotherapy.<sup>5,6</sup> Triple-hit lymphomas are rare, and may occur *de novo* or transform from low-grade lymphomas, most commonly follicular lymphoma. In a study of 11 patients with triple-hit lymphoma, 4 patients (36%) had a history or concurrent follicular lymphoma, and 5 patients (45%) died within a year. Involvement of extranodal sites included bone marrow, spleen, tonsil, bladder and

testicle, and no orbital involvement was reported.<sup>6</sup>

We report a patient with unusual clinical presentations of a triple-hit lymphoma transformed from systemic FL. The transformation presented as an isolated orbital mass after 9-year remission of FL, and the patient had no B symptoms or significantly elevated LDH to cause clinical suspicion of transformation. Subsequent work-up demonstrated only focal uptake in lymph nodes on PET-CT, and bone marrow staging showed < 5% involvement by a low-grade FL.

It is important to perform FISH analysis on large B-cell lymphoma as double- or triple-hit lymphomas require more aggressive chemotherapy. Additionally, discordant histology occurs in up to 50% of DLBCL between bone marrow and extramedullary sites, most commonly characterized by low-grade FL in the bone marrow but DLBCL in the extramedullary sites, as exemplified in this case. Therefore, extramedullary tissue biopsy is important in assessment of lymphoma, particularly for possible progression or transformation of low-grade lymphoma.

DLBCL is typically treated by R-CHOP chemotherapy. However,

double- or triple-hit lymphomas are highly aggressive, and no standard treatment has been established. Our patient was treated with R-ICE and R-GD followed by a two-year maintenance on rituximab. She was in remission for three years but died of cardiac failure.

In conclusion, we presented an unusual case of transformation of FL to a high-grade, triple-hit B-cell lymphoma that presented as an isolated orbital mass without systemic symptoms, significant lymphadenopathy or concordant large cell lymphoma in the bone marrow. Biopsy of the orbital mass served as the initial recognition of the triple-hit lymphoma transformed from the FL after 9 years in remission. Early recognition of these high-grade B-cell lymphomas is important for prompt treatment. Although these patients are often refractory to current chemotherapy, rapidly emerging immunotherapeutic approaches, such as chimeric antigen receptor T-cell therapy (CAR T-cell therapy), may become an effective therapeutic option for patients with high grade B-cell lymphoma.

### 3. Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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### Conflicts of interest

The following authors have no financial disclosures: XYZ, XL, KR, YHC.

### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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### References

1. Casulo C, Burack WR, Friedberg JW. Transformed follicular non-hodgkin lymphoma. *Blood*. 2015;125:40–47.
2. Pedersen MO, Gang AO, Poulsen TS, et al. Double-hit bcl2/myc translocations in a consecutive cohort of patients with large b-cell lymphoma - a single centre's experience. *Eur J Haematol*. 2012;89:63–71.
3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the world health organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.
4. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol*. 2015;170:504–514.
5. Dunleavy K. Aggressive B cell lymphoma: optimal therapy for myc-positive, double-hit, and triple-hit DLBCL. *Curr Treat Options Oncol*. 2015;16:58.
6. Wang W, Hu S, Lu X, et al. Triple-hit B-cell lymphoma with MYC, BCL2, and BCL6 translocations/rearrangements: clinicopathologic features of 11 cases. *Am J Surg Pathol*. 2015;39:1132–1139.