

# Double hit lymphoma presenting as haemophagocytic lymphohistiocytosis

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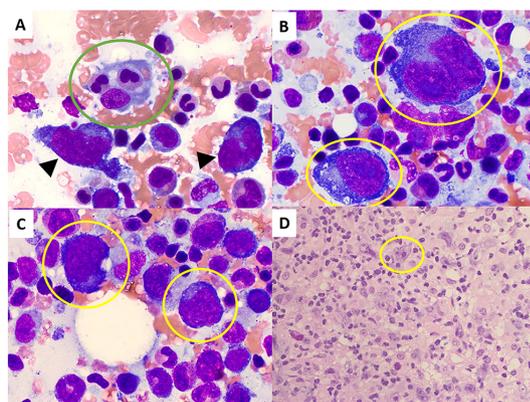
## DESCRIPTION

A 67-year-old woman with history of severe rheumatoid arthritis and use of multiple biologics including infliximab, tocilizumab and abatacept presented with fever of 39.1°C and severe pancytopenia (white blood cell count (WBC)= $1.0 \times 10^9/L$ , absolute neutrophil count (ANC)= $0.55 \times 10^9/L$ , haemoglobin=8.7 g/dL, platelets= $46 \times 10^9/L$ ). As part of the pancytopenia evaluation, imaging (CT of the chest, abdomen and pelvis) showed diffuse lymphadenopathy. Further evaluation revealed an elevated ferritin (8564 ng/mL), hypofibrinogenemia (fibrinogen=95 mg/dL), elevated triglycerides (399 mg/dL) and a soluble interleukin 2 receptor level of 41 167 units/mL, satisfying diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH). A subsequent bone marrow biopsy also revealed morphological evidence of haemophagocytosis (figure 1A), in addition to a population of very large and atypical mononuclear cells with markedly irregular, folded nuclear contours, prominent nucleoli and moderate amounts of cytoplasm (figure 1B,C). A similar large cell infiltrate was identified in the left axillary lymph node, causing complete effacement of nodal architecture (figure 1D). Immunohistochemistry performed on tissue sections revealed the neoplastic cells to be positive for PAX5 and CD20, both B-cell markers, in addition to CD45, BCL6, MUM1 and weak CD30. BCL2 and T-cell marker CD2 were also aberrantly expressed. The neoplastic cells were negative for CD10, CD15, MYC and cyclin D1. Ki-67, a proliferation marker, was positive in more than 90% of the neoplastic cells. Fluorescence

in situ hybridisation showed rearrangements of MYC and BCL6, confirming a diagnosis of double hit lymphoma (DHL). She was treated with dose adjusted-etoposide + prednisone + vincristine (Oncovin) + cyclophosphamide + doxorubicin (Hydroxydaunorubicin) - rituximab (DA-EP-OCH-R). Furthermore, she had low-level central nervous system involvement in her cerebrospinal fluid (CSF) by flow cytometry which was treated with intrathecal therapy resulting in clearing of her CSF. Her 'HLH indices' clinically resolved after one cycle of chemotherapy, with normalisation of her counts. She is now doing well clinically, and recent positron emission tomography scan shows complete response to therapy with resolution of all abdominal and thoracic adenopathy.

Defects in cytotoxic T cells and natural killer cells are seen in all cases of HLH.<sup>1</sup> HLH is typically associated with T-cell malignancies, with only rare reported associations with B-cell lymphomas.<sup>1</sup>

The current WHO definition of DHL requires the occurrence of a MYC rearrangement along with BCL2 or BCL6 rearrangements.<sup>2</sup> Patients typically have advanced stage disease, with elevated lactate dehydrogenase, high international prognostic index scores and poor outcomes.<sup>2</sup> Multiple retrospective series show that rituximab (Mabthera) - cyclophosphamide + doxorubicin (Hydroxydaunomycin) + vincristine (Oncovin) + prednisolone (R-CHOP) is an insufficient therapy in patients with DHL with median overall survival of 10 months or less.<sup>2</sup> Although there were no detectable differences between the augmented regimens, the use of R-CHOP had inferior survival compared with all other treatments with a HR of 0.53. DA-EPOCH-R has been associated with high overall response rates and longer event-free



**Figure 1** (A) 100× Wright-Giemsa haemophagocytosis by a macrophage (circled); (B,C) 100× Wright-Giemsa large neoplastic cells (circled) and (D) 40× H&E left axillary lymph node.

## Learning points

- ▶ Fever, cytopenias and elevated ferritin should raise strong clinical suspicion for haemophagocytic lymphohistiocytosis (HLH), a rare but potentially fatal disorder that requires prompt recognition and treatment.
- ▶ Therapy of secondary HLH is based on the treatment of its underlying aetiology: the high-grade lymphoma in this case.
- ▶ Double hit lymphomas are aggressive lymphomas with frequent central nervous system involvement, poor overall prognosis and represent an unmet medical need.



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survival.<sup>2</sup> Along with the choice of the optimal chemoimmunotherapy backbone, the role of high-dose therapy in DHL is undefined and should be considered on a case-by-case basis.<sup>2</sup>

In summary, this is the first documented case of DHL presenting as HLH (to our knowledge). While ongoing advances in targeted MYC and BCL2 inhibition with agents such as venetoclax show promising results,<sup>3</sup> this represents an unmet medical need in lymphoma.

**Contributors** XIR wrote the paper, prepared clinical images for publication, prepared manuscript for publication and approved the manuscript. LJM obtained and interpreted clinical images for publication, prepared clinical images for publication and approved the manuscript. JHS treated the patient, analysed the data providing clinical interpretations and approved the manuscript. SDP treated the patient, analysed the data providing clinical interpretations, wrote the paper and approved the manuscript.

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