A 68-year-old patient was admitted to our hospital with a short history of constipation and dyspnea. Cytology of the pleural effusion revealed large blastoid B cells. Positron emission tomography/computed tomography scan showed extensive fluorodeoxyglucose activity. In the bone marrow aspirate, large blasts with deeply basophilic cytoplasm and numerous vacuoles resembling Burkitt cells (panel A) were present. Cytogenetic and fluorescence in situ hybridization analysis showed MYC, BCL2 (double hit), and BCL6 (triple hit) rearrangements within a complex karyotype (panel B), seen in about 5% to 15% of diffuse large B-cell lymphomas (DLBCL). It was therefore classified according to the World Health Organization as a B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma due to the distinct cytogenetic alterations. Because of the aggressive behavior of the disease, we treated with 3 cycles of rituximab hyper-CVAD/rituximab high-dose methotrexate and 6 intrathecal chemoprophylaxes. Positron emission tomography/computed tomography scan showed complete resolution and the patient was well. However, disease recurrence was documented shortly after. The patient died despite reinduction with rituximab-DHAP.

Double- and triple-hit lymphomas are chemosensitive aggressive B-cell lymphomas, but unlike Burkitt lymphoma and DLBCL they have a very high recurrence rate and are almost always fatal. Proper molecular characterization of lymphomas to determine prognosis is very important for patient advice and treatment decision.
Double hit, triple hit—look for it

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