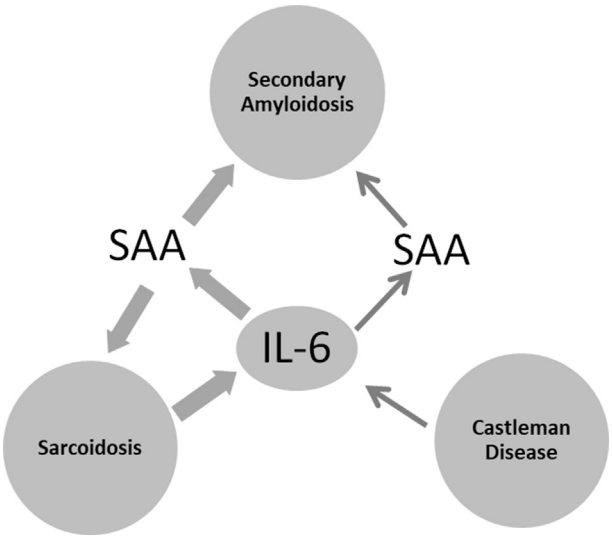

Fig. 2 The presumptive pathogenesis of reactive lymphadenopathy with concurrent Castleman disease, sarcoidosis and reactive amyloidosis. IL-6 might trigger persistent overproduction of SAA protein which may contribute to concomitant Castleman disease, sarcoidosis and secondary amyloidosis.

Secondary type AA amyloidosis is characterised by extracellular deposition of insoluble proteins which may impact the function of involved organs. AA amyloid deposition is known to complicate active chronic conditions seen in inflammatory diseases and malignancies. Serum amyloid A protein (SAA) is the precursor protein for reactive/secondary amyloidosis. One study indicated that SAA might be responsible for sarcoidosis.[10] In that study, the authors showed high levels of this protein in the granulomas of sarcoidosis and confirmed that SAA protein was the cause of sustained chronic inflammation of affected patients.[11] In the patient we report persistent chronic inflammatory disease as a result of Castleman disease and sarcoidosis, driving persistently elevated IL-6 levels, which might explain the overproduction of SAA protein leading to disease progression and manifestations of secondary reactive amyloidosis.[12] Given that SAA protein might have a pathogenic role in the granulomatous inflammation of sarcoidosis through a sustained inflammatory reaction, the possibility of increased SAA triggering sarcoidosis in this patient should be also considered (Fig. 2). Overall, SAA might contribute to concomitant Castleman disease, sarcoidosis and secondary amyloidosis.

In conclusion, Castleman disease can be rarely associated with sarcoidosis and secondary amyloidosis. Our report extends the literature by contributing a case of concurrent idiopathic Castleman disease, sarcoidosis, and amyloidosis. Dysregulation of the immune system, sustained chronic inflammation, and SAA protein may be the underlying aetiology of these concomitant disorders/diseases.

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TdT-positive high grade B-cell lymphoma transformed from grade 3B follicular lymphoma in an HIV-positive patient

Sir,

Follicular lymphoma (FL) is graded as low (grades 1 and 2) and high (grades 3A and 3B) based on the number of centroblasts.[1] Low grade FLs are known to be clinically indolent, but have a natural tendency to recur or transform into more aggressive and diffuse neoplasms, usually diffuse large B-cell lymphoma (DLBCL).[2] Grade 3B FL is thought a different entity from grade 1-3A FL because its molecular, cytogenetic and immunophenotypic features resemble, in part, cases of DLBCL.[3] While progression from lower to higher grade is common in FL, blastoid transformation is rare.[4]

Human immunodeficiency virus (HIV) infection is associated with a higher risk of lymphoma development. HIV-associated NHLs are a heterogenous group, but are predominantly aggressive B-cell lymphomas.[5] DLBCL and Burkitt lymphoma (BL) are the most common subtypes, whereas FLs and peripheral T-cell lymphomas are rarely associated with HIV infection.[6]

In this report, we describe a patient with HIV infection who had grade 3B FL associated with *BCL6* rearrangement. The lymphoma underwent transformation into a Terminal deoxynucleotidyl transferase (TdT)+ high grade B-cell lymphoma with acquired *MYC* rearrangement during disease evolution.

The patient was a 44-year-old man with a diagnosis of HIV infection in the 1990s, intermittently on highly active antiretroviral therapy (HAART), and presenting with cervical lymphadenopathy. Laboratory workup revealed a CD4+ T-cell count of 87/μL (normal 500−1500/μL). Computed tomography (CT) scan showed generalised lymphadenopathy and marked diffuse gastric wall thickening.

The patient initially underwent an excision of the left cervical lymph node. Histological sections showed complete effacement of the nodal architecture by back-to-back follicles that lacked the usual polarisation and tingible-body macrophages (Fig. 1A). Sheets of large centroblasts were identified in the neoplastic follicles (Fig. 1B,C). Immunohistochemical analysis showed neoplastic cells positive for CD19, CD20, CD79a, PAX5, BCL2, BCL6 (weak) and MUM1/IRF4 (Fig. 1D−I), and negative for CD3, CD5, CD10, CD34, CD43, CD138, EMA, TdT and HHV8 (Fig. 1). *In situ* hybridisation (ISH) for EBV-encoded RNA (EBER) was negative. CD21 highlighted the residual follicular dendritic meshworks within follicles. The antibody specific for Ki-67 showed a proliferation activity of 60−70% (Fig. 1E). Concurrent flow cytometric immunophenotyping showed an aberrant B-cell population with monotypic kappa expression

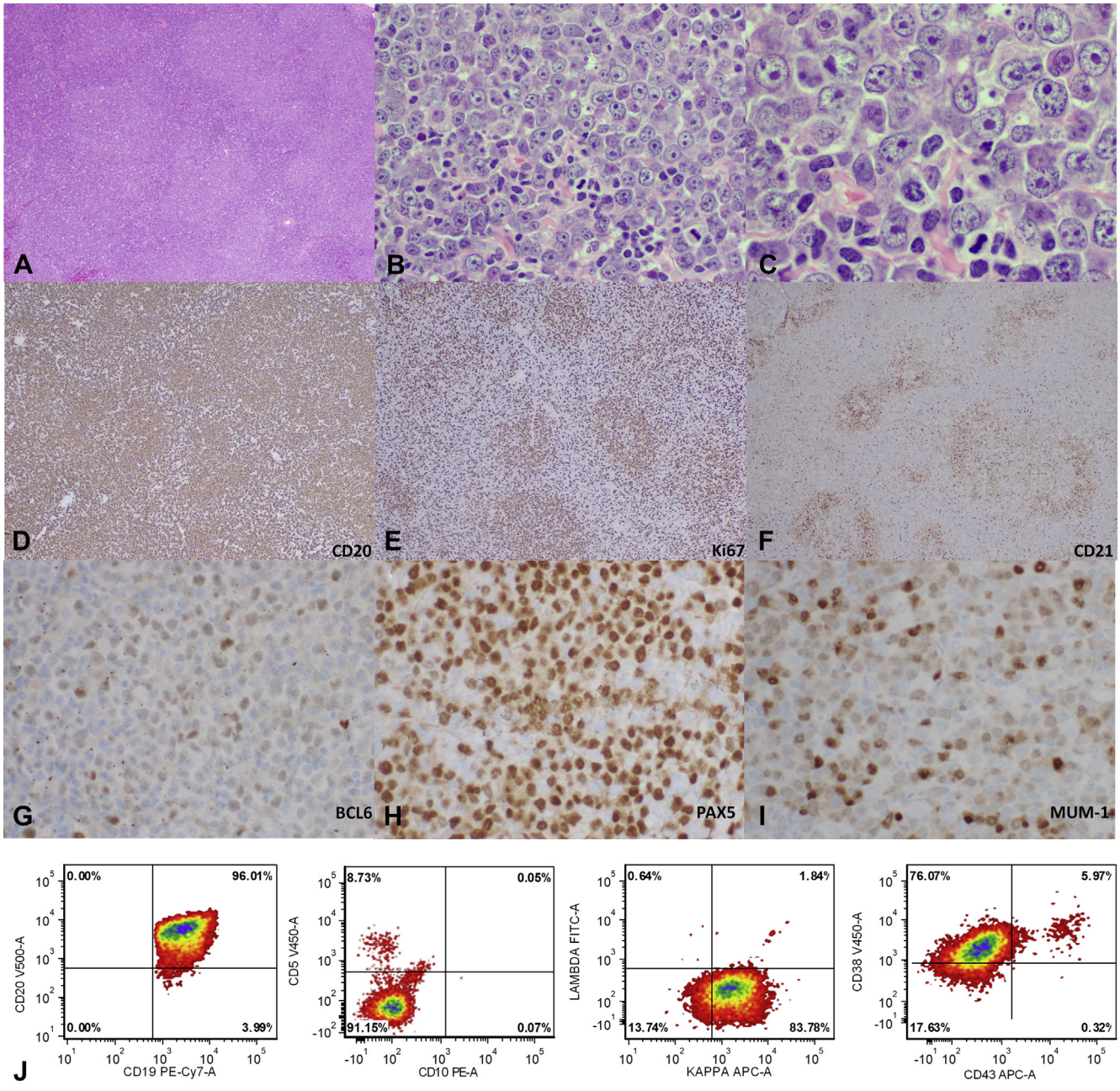

Fig. 1 Histological and immunophenotypical findings of cervical lymph node. (A−C) H&E stained sections show complete effacement of the nodal architecture by focal sheets of large neoplastic cells. (D−I) Immunohistochemical stains (D, CD20; E, Ki-67; F, CD21; G, BCL6; H, PAX5; I, MUM-1). (J) Flow cytometry showing an aberrant B cell population with monotypic kappa light chain expression.

(Fig. 1J). The morphology combined with immunophenotype was diagnostic of a grade 3B FL. Fluorescence *in situ* hybridisation (FISH) studies demonstrated *BCL6* rearrangement with no evidence of *IGH/BCL2*, *IGH/MYC,* or *DUSP22-IRF4* rearrangement. Additional studies showed that the patient's cerebrospinal fluid (CSF) and bone marrow were negative for lymphoma.

After the diagnosis of high grade follicular lymphoma, the patient received dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-R-EPOCH) for 6 cycles. At the same time, the patient remained on HAART. Fluoro-deoxyglucose (FDG)-positron emission tomography (PET) scan after therapy showed minimal residual FDG uptake of multiple lymph nodes and gastric wall lesion, suggestive of a good response.

Four months after DA-R-EPOCH treatment, the patient presented with headaches and blurry vision. His CD4+ T-cell count was 126/μL. Cytospin preparations of CSF were cellular, composed of numerous intermediate to large-sized malignant cells with a high nuclear-to-cytoplasmic ratio, fine chromatin and prominent nucleoli (Fig. 2A). Flow cytometry of the CSF fluid showed B lymphoid cells with

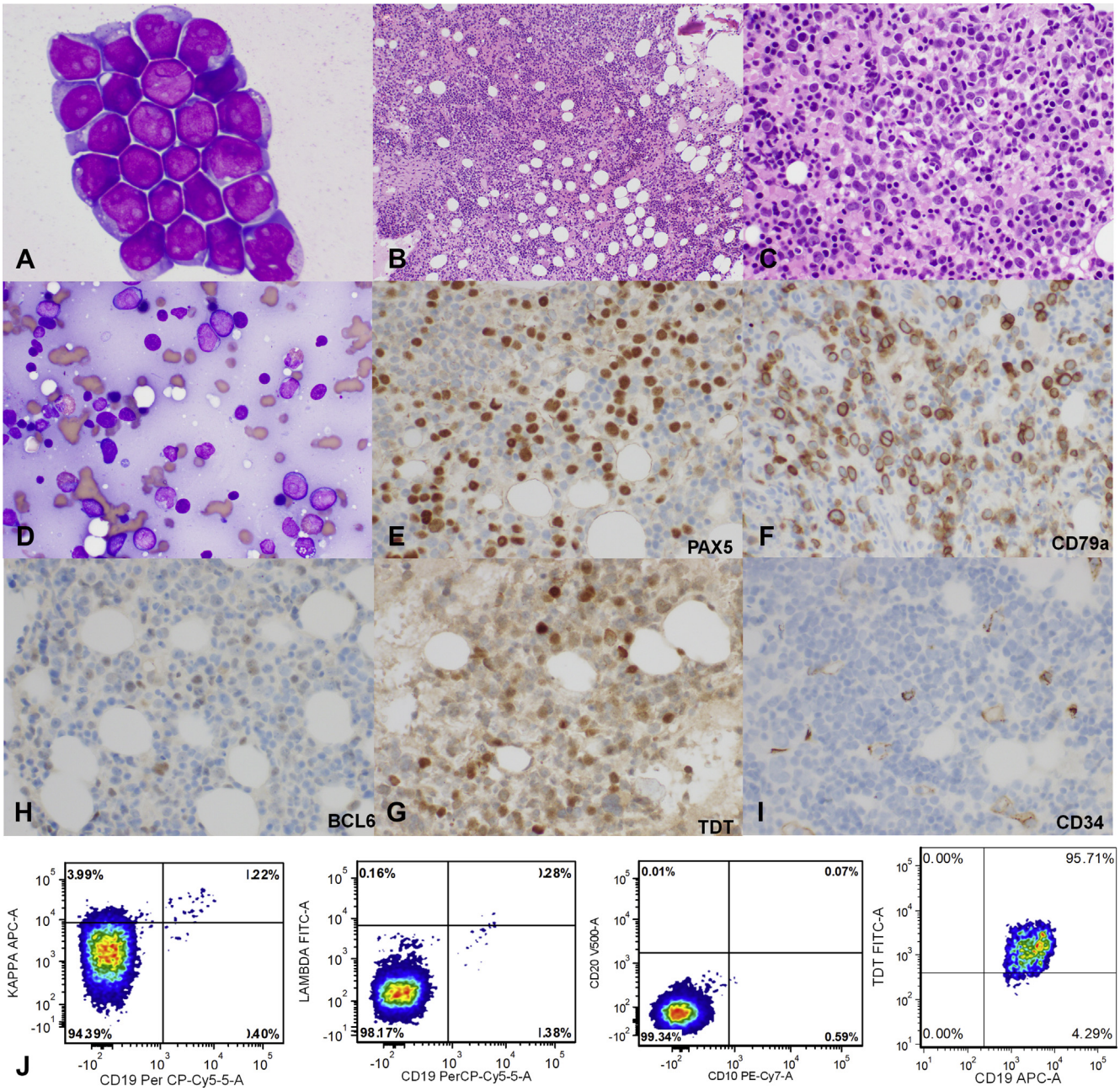

Fig. 2 Histological and immunophenotypical findings of cerebrospinal fluid and bone marrow. (A) Diff-Quik stained cytospin preparations of cerebrospinal fluid show numerous malignant cells with fine chromatin and prominent nucleoli. (B) Bone marrow biopsy demonstrates an 80−90% cellularity and 20−30% of the cells were intermediate-large sized abnormal lymphoid cells with blastoid chromatin in an interstitial pattern. (C) Bone marrow aspiration showed rare atypical neoplastic cells with morphology similar to the cells found in the CSF. (D−I) Immunohistochemical stains performed on the core biopsy. The malignant cells are positive for (D) PAX5, (E) MUM1, (F) CD79a, (G) TdT, (H) BCL6 (weak), and negative for (I) CD34. (J) Flow cytometry of the bone marrow aspiration reveals a neoplastic cell population positive for CD19 and TdT, and negative for CD10, CD20, kappa and lambda.

TdT expression. FISH analysis revealed rearrangements of *BCL6*/3q in 89% and *MYC*/8q in 93% of the cells; and a gain of *BCL2*/18q in 71% of nuclei.

Peripheral blood and bone marrow aspirate smears (Fig. 2B) showed neoplastic cells with morphology similar to that described in the CSF. Bone marrow trephine biopsy demonstrated a hypercellular (80−90%) marrow within which 20−30% of the neoplastic cells were arranged in an interstitial pattern (Fig. 2C,D). Immunohistochemical analysis of marrow biopsy showed that the neoplastic cells were positive for CD79a, PAX5, MUM1/IRF4, BCL6 and TdT, and negative for CD34 and CD10 (Fig. 2E−I). Flow cytometric analysis of marrow aspirate showed a neoplastic population positive for CD19, partial CD20 and TdT (Fig. 2J). Conventional cytogenetic analysis showed a complex male karyotype: 54,XY,+del(X)(q22q27),+1,add(1)(p12),+der(2; 5)(p10; q10),+3,add(3)(p12),t(3; 22) (q27; q11.2),+6,add(6)(q13),+7,add(7)(q32),+10,add(10)(q25),+12,add(12)(q24.3),t(14; 17) (q32; q25)[7]/46,XY[13]. FISH analysis was positive for *MYC* and *BCL6* rearrangements. A diagnosis of TdT-positive high grade B-cell lymphoma with *MYC* and *BCL6* rearrangements was rendered on both the CSF and bone marrow specimens. Following this new diagnosis, the patient was placed on salvage chemotherapy with rituximab, dexamethasone, high-dose Ara-C-cytarabine and cisplatin (R-DHAP) and intrathecal methotrexate. He had significant clinical improvement after two cycles of R-DHAP and intrathecal methotrexate.

We assessed the neoplasms for *IGH* and *IGK* rearrangements using polymerase chain reaction (PCR)-based methods to determine whether the FL in the initial lymph node specimen and the TdT-positive high grade B-cell lymphoma in the bone marrow were clonally related. In the initial left cervical lymph node specimen, we identified a clonal *IGK* rearrangement with no evidence of clonal *IGH* rearrangement. The bone marrow specimen showed both *IGH* and *IGK* clonal rearrangement. The clonal *IGK* rearrangement in the initial bone marrow specimen was similar to that of cervical lymph node specimen, indicating both neoplasms were likely derived from the same clone.

Our case is an HIV-positive patient with a grade 3B t(14;18)-negative FL associated with *BCL6* rearrangement who subsequently developed TdT+ blastoid transformation with an acquired *MYC* rearrangement. There are rare reported cases of patients with low grade FL who developed subsequent TdT+ B-cell acute lymphoblastic leukaemia with *MYC* and *BCL2* translocations.[7] However, our case appears to be unique as this transformed TdT+ high grade lymphoma was associated with *BCL6* and *MYC* rearrangements.

During the patient's clinical course, his lymphoma underwent clonal evolution to acquire blastoid features, *MYC* translocation and TdT expression. The mechanisms to explain this rare form of transformation in the patient we report are unknown, but it seems likely that HIV infection and the severe immunosuppression may have facilitated this unusual sequence of events. There is currently no existing consensus to determine the best terminology for the neoplasm in this patient. Given the morphology, immunophenotype, and cytogenetic changes, it seems reasonable to propose four possible designations: (1) high grade B-cell lymphoma (HGBCL) with *MYC* and *BCL6* rearrangement; (2) B lymphoblastic leukaemia/lymphoma; (3) lymphoblastic transformation of FL; and (4) TdT+ DLBCL.

HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangement was introduced in the revised World Health Organization (WHO) classification published in book form in 2017.[8] These neoplasms are usually highly aggressive clinically and can be further subclassified into double or triple hit lymphoma depending on the number of gene rearrangements. Double hit lymphomas with *MYC* and *BCL2* rearrangement represent 67% of cases, triple hit lymphomas with *MYC*, *BCL2* and *BCL6* rearrangement comprise 21%, and lastly, double hit lymphomas with *MYC* and *BCL6* rearrangement account for 14% of all HGBCLs.[9] Cases of HGBCL can morphologically resemble DLBCL or they may have a blastoid or Burkitt-like appearance. A subset of cases of HGBCL with *MYC* and *BCL2* and/or *BCL6* may have a history of FL, but according to the WHO classification, FLs with a double or triple hit genetics are not included in this category. TdT expression, however, is not considered a part of this category in the revised WHO classification.

Based on TdT expression, one might consider designating this neoplasm as B lymphoblastic leukaemia/lymphoma. Although the patient we present had CSF and bone marrow involvement at diagnosis, this classification is not a good fit due to his history. The patient age, history of HIV infection, and history of FL would be highly unusual in a patient with B lymphoblastic leukaemia/lymphoma. While possible, *MYC*, *BCL2*, and *BCL6* rearrangements are also exceedingly rare in B lymphoblastic leukaemia/lymphoma.[10]

B-cell lymphoblastic transformation of FL is currently the preferred designation in the WHO classification and such cases have been reported previously by Geyer *et al.*[11] These patients present with FL, and after a variable but often long interval with many relapses, they acquire TdT expression. Although we have no specific criticisms of the underlying science of this approach, in our experience the change in terminology from FL to B-cell lymphoblastic transformation of FL can be a challenge as follows. In clinical protocols designed for patients with FL who undergo histological transformation and may be eligible for chimeric antigen receptor (CAR) T-cell therapy, typically the designation of diffuse large B-cell lymphoma is required.

The last option is the designation of TdT+ DLBCL. Although this terminology is somewhat better than B lymphoblastic leukaemia/lymphoma, this term does not seem to be a good fit as has been discussed by Ok and colleagues.[12] As discussed in their manuscript, patchy or variable TdT expression seems to be an insufficient reason to change the designation of a neoplasm from DLBCL of germinal centre B-cell type, to lymphoblastic transformation of FL.

In summary, in our opinion it is most reasonable to include this transformed lymphoma as HGBCL with *MYC* and *BCL6* rearrangement, transformed from FL, despite the expression of TdT. TdT expression in this context likely suggests a distinctive pathway for high grade transformation of FL.

Regardless of the designation employed for this neoplasm, we believe reporting this case can be helpful in calling this issue to the attention of others, with the hope that additional cases will be reported and perhaps lead to a consensus for the optimal terminology for cases such as that described in this report.

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Anti-Xa levels with low molecular weight heparin calibrator can be used to exclude significant apixaban effect

Sir,

Apixaban levels can be measured using an anti-Xa assay with apixaban-specific calibrator. However, as apixaban levels are infrequently required and the specific calibration and control material has limited stability at room temperature, the commitment of resources to perform an apixaban level may not be deemed justifiable at some laboratories. Therefore, they may not offer the assay, or limit availability to restricted hours of operation. In contrast anti-Xa levels for low molecular weight heparin (LMWH) are more commonly requested, and easier to perform after hours. We sought to correlate apixaban levels with anti-Xa-LMWH, with the aim of identifying a threshold anti-Xa-LMWH level that would allow exclusion of therapeutic apixaban levels in emergency situations.

We collected blood from 28 patients who had been taking apixaban for at least 3 days, and performed anti-Xa using STA-Liquid Anti-Xa kit with STA-Multihep calibrator and STA-apixaban calibrator (Stago, France). The demographic data are shown in Table 1, and the correlation curve is shown in Fig. 1.

At lower levels of apixaban, there is a near-linear relationship between apixaban level and anti-Xa-LMWH. These findings are consistent with previous studies demonstrating a linear relationship between anti-Xa-LMWH activity and apixaban levels in this range measured using either liquid chromatography tandem mass spectrometry (LC-MS/MS) or an apixaban-calibrated anti-Xa assay.[1–3] The 'on target' range for apixaban is quoted as being 20–100 ng/mL for 2.5 mg twice daily dosing and 30–412 ng/mL for 5 mg dosing twice daily.[4–6] According to our results, 20 ng/mL correlates with an anti-Xa-LMWH of 0.40 IU/mL. Hence, an anti-Xa-

Table 1 Demographics

Apixaban dose	2.5 mg BD	5 mg BD	All samples
n	17 (61%)	11 (39%)	28 (100%)
Gender, *n*			
Male	11 (65%)	5 (45%)	16 (57%)
Female	6 (35%)	6 (55%)	12 (43%)
Age, years			
Median	66	59	65
Range	47–83	18–87	18–87
Weight, kg			
Median	88	76	81
Range	55–128	50–130	50–130
Creatinine clearance, mL/min			
Median	84.1	100.4	93.2
Range	39.8–115.5	50–136.1	39.8–136.1
Time since ingestion, hours			
Median	7.25	7.42	7.25
Range	4.4–8.75	5–10.17	4.4–10.17
Apixaban level, ng/mL			
Median	48.5	100.9	70.3
Range	21–143.3	30.8–202.5	21–202.5