Dear Editor,

Hodgkin lymphoma (HL) comprises two major entities: classic Hodgkin lymphoma (CHL) in > 90% of cases and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) in the remaining 5–10%. Both are of B cell origin, but only NLPHL generally retains the B cell programme [1–3]. Only a minority (4–5%) of NLPHL are associated with Epstein-Barr virus (EBV, human herpesvirus 4 (HHV-4)), whereas in CHL, EBV can be found in up to 50% of cases [1–3]. EBV infection affects > 90% of adults worldwide. Primary infection is mostly asymptomatic but leads to a persistent latency infection [4]. EBV dormancy is characterised by specific latency programmes with differential expression of viral non-coding RNAs (e.g. EBV-encoded RNAs, EBERs), latent membrane proteins (LMPs) and EBV-nuclear antigens (EBNAs). EBERs are found in all latency states, whereas LMPs and EBNAs are variably expressed [5, 6]. Latency type II with expression of LMP1 and positive in situ hybridization (ISH) for EBERs is nearly ubiquitous in EBV-associated CHL. The latency pattern for EBV-positive NLPHL is not precisely established [1, 2, 6, 7].

We present a case of NLPHL with an unusual EBV latency type. We received a formalin fixed paraffin-embedded cervical lymph node of a 60-year-old female patient of Iranian descent. She presented with B-symptoms, cervical, abdominal and inguinal lymphadenopathy and splenomegaly. The past medical history and laboratory parameters were largely unremarkable. Lymph node architecture was effaced by a nodular infiltrate composed predominantly of small lymphocytes, histiocytes, sparse eosinophils and intermingled larger atypical cells, some with features of Hodgkin- and Reed-Sternberg cells, and others of LP cells (Fig. 1a, b, c). Morphology prompted a differential diagnosis of nodular sclerosis CHL vs the rare case of NLPHL with occasional eosinophils. Atypical cells co-expressed CD20 (Fig. 1d), CD79a, CD75, OCT-2, BOB.1 and BCL6, while CD30 was detected only in single, non-neoplastic bystander cells. CD21 highlighted the presence of follicular dendritic cell meshworks with embedded tumour cells. Immunohistochemistry for PD1 identified rosettes of PD1-positive T cells that surrounded LP-cells. Clonality analysis employing the BIOMED-2 protocol ruled out the presence of a clonal T cell population. These findings prompted a diagnosis of NLPHL and ruled out all differential diagnoses. Repeated immunostaining for LMP-1 was negative (Fig. 1e). Unexpectedly, a majority of tumour cells harboured EBER transcripts, albeit a minority remained negative (Fig. 1f), indicating a latency gene expression pattern other than type II, potentially type I. Moreover, sparse EBER-ISH-positive small lymphoid cells of the microenvironment were detectable. The literature covering EBV in NLPHL is limited [2, 8, 9]. Positive EBER-ISH and LMP1 expression have been reported, as well as positive EBER-ISH but negativity for LMP1 and even a case with probably artificially negative EBER-ISH and positivity for LMP1 [2, 8, 9]. Nonetheless, the available literature implies that unlike CHL, NLPHL is not unequivocally associated with a certain EBV latency gene expression pattern. We postulate that NLPHL demonstrates a broad spectrum of EBV latency patterns and that it is worthwhile to examine these in order to gain further insights into the complexity of this disease.
Authors’ contributions MTR, EMH, IA and AR were responsible for pathology and manuscript preparation, and CL provided anonymised clinical data.

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Compliance with ethical standards

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