Fig. 2 Diffuse proliferation of neuroendocrine micronests in colonic mucosa. (A) Scattered small nests of neuroendocrine cells in the lamina propria, embedded in the neural tissue of diffuse ganglioneuromatosis, but distant from the neuroendocrine tumour component. (B) Chromogranin immunostain confirms the neuroendocrine nature of the abnormal cell nests in the lamina propria.

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High-grade B-cell lymphoma with concurrent expression of CD5 and cyclin D1 and *MYC* rearrangement

To the Editor,

High-grade B-cell lymphoma not otherwise specified (HGBL-NOS), according to the World Health Organization (WHO) 2017 Classification, represents a heterogeneous group of extremely aggressive neoplasms defined by blastoid

cytology, lacking the double or triple hit (DH/TH) rearrangements of *MYC* and *BCL2* and/or *BCL6* genes.¹ Rigorous immunohistochemical and molecular characterisation of malignant lymphomas with high-grade blastoid features is critical to distinguish HGBCL-NOS from DH/TH lymphomas, Burkitt lymphoma (BL), lymphoblastic lymphoma (LL) and blastoid variant of mantle cell lymphoma (BVMCL). We describe here a rare case of HGBCL-NOS with *MYC* rearrangement only and exceptional co-expression of CD5 and cyclin D1. We discuss the dilemma of differential diagnosis, explaining that this uncommon phenotype represents a new observation, not having been described yet in HGBCL-NOS in the current literature.

A 69-year-old female patient was admitted to St Eugenio Hospital of Rome with severely compromised general conditions, weight loss, fever, and abdominal discomfort. A total body computed tomography (CT) scan detected several bulky nodal masses in the retroperitoneum (Fig. 1A). Neither blood count nor blood smear showed any leukaemic picture or circulating abnormal cells. Therefore, a core needle biopsy was performed. Unfortunately, we could not assess the tissue by flow cytometry. Histopathological examination showed a diffuse infiltration of medium sized tumour cells with scant amphophilic/basophilic cytoplasm, round to oval nuclei with fine chromatin, small single (sometimes centrally located) or multiple basophilic nucleoli. Apoptotic bodies were present without a clear-cut 'starry sky' appearance. Numerous mitotic figures were also detected (Fig. 1B,C), and the proliferation index assessed by Ki-67 immunostaining reached 100% (Fig. 2). These findings were considered compatible with the so-called blastoid morphology. Immunohistochemical staining revealed the diffuse expression of PAX5, CD20, CD10 and IRF4/MUM1 (Fig. 1); a subset of tumour cells expressed BCL6 (Fig. 1), however staining for TdT and CD34 was negative. The lymphoma cells had diffuse and strong expression of BCL2 (Fig. 1) and exhibited high nuclear immunostaining for c-MYC in approximately 90% of the cells (Fig. 2). EBV-encoded RNA (EBER) was also negative. Follicular dendritic cell meshwork evaluated by CD23 staining was absent. Surprisingly, both CD5 and cyclin D1 were widely expressed by the neoplastic cells. Of note,

Fig. 1 (A) A total body CT detected several bulky nodal masses in the pelvic retroperitoneum located on left iliac bone wing (asterisk). (B) The diffuse neoplastic proliferation was composed by mid-sized tumour cells with round nuclei with fine chromatin, small multiple and single nucleoli with scant cytoplasm; some karyorrhectic debris was also present (H&E; C, higher power). Numerous mitotic figures were also detected (red arrows). These findings were considered compatible with blastoid morphology. CD20, BCL2, CD10 and IRF4/MUM1 were strongly expressed by tumour cells. Only a small subset of the cells expressed BCL6. SOX11 was absent. Immunohistochemical typing revealed diffuse expression of CD5 whereas cyclin D1 was present in 80–90% of the nuclei.

CD5 was positive on all the tumour cells, whereas cyclin D1 was present in 80–90% of the nuclei (Fig. 1). Therefore, SOX11 immunostaining was conducted and the result was negative (Fig. 1). Due to strong co-expression of CD5 and cyclin D1, we first favoured a diagnosis of BVMCL.

To confirm our hypothesis, fluorescence *in situ* hybridisation (FISH) analysis by *CCND1/IGH* Dual Color Dual Fusion Probe and *CCND1* Break Apart Probe were both negative for *CCND1* gene rearrangement (Fig. 2B). Furthermore, there were no extra *IGH* signals to suggest a rearrangement with an unknown partner. Thus, BVMCL was excluded. FISH analysis by *MYC* Dual Color Break Apart Probe showed *c-MYC* gene rearrangement (Fig. 2A). Two additional FISH tests with *BCL2* Dual Color Break Apart Probe and *BCL6* Dual Color Break Apart Probe were conducted, and both were negative, excluding a DH/TH lymphoma. Table 1 lists the antibodies and probes used.

Considering the blastoid cytomorphology and phenotype as well as the results of FISH tests, the lymphoproliferative disease was classified as HGBCL-NOS with *MYC* translocation only, also called single-hit lymphoma (SHL), according to the 2017 update of the WHO Classification. In addition, a brief discussion regarding the unusual co-expression of both CD5 and cyclin D1 was added in the pathology report, explaining that this uncommon phenotype represents a finding of new observation, not having been described yet in HGBCL-NOS by the current literature. Bone marrow core biopsy revealed trilineage haematopoiesis without involvement by malignant B cells. The serious general condition of our patient meant that she could not tolerate intensive chemotherapy, so only

supportive care was provided to the patient who died within 3 months of the diagnosis.

This new category of HGBCL-NOS is reserved for a group of extremely aggressive malignant B-cell lymphomas with blastoid morphology and without cytogenetic evidence for DH/TH lymphomas. However, ‘blastoid morphology’ remains an extremely subjective terminology that includes a rather broad morphological spectrum, ranging from BL, LL, DH/TH lymphomas to BVMCL. Occasionally, the morphology of these different aggressive lymphomas may show overlapping features.

Although in our case the morphology of the neoplastic cells was not typical for BL and LL, DH/TH lymphomas and BVMCL could still be suspected. Both BL and LL were excluded by the significant expression of *BCL2* and by the absence of both TdT and CD34 staining, respectively. DH/TH lymphoma was also excluded by the absence of both *BCL2* and/or *BCL6* translocations. Notwithstanding, the case we describe here shows that HGBCL-NOS may be a mimic of BVMCL, and differentiating these two diseases could be very troublesome using only morphological and immunohistochemical workups. In fact, the uncommon and misleading expression of both CD5 and cyclin D1 in our case represents a diagnostic trap, because in daily practice FISH confirmation for *CCND1* gene rearrangement would not be mandatory for supporting a diagnosis of mantle cell lymphoma (MCL) with otherwise typical phenotype.² Accordingly, we could have considered the presence of both CD5 and cyclin D1 as sufficient evidence to diagnose BVMCL, thus skipping FISH analysis for *CCND1*. Furthermore,

Fig. 2 The lymphoma cells exhibited high nuclear immunostaining for c-MYC (around 90%) whereas Ki67 reached 100% (inset). (A) FISH analysis for c-MYC 8q24 by Dual Colour Break-Apart Probe showed MYC gene rearrangement. MYC rearrangement-positive tumour cells show one yellow fusion signal, one orange and one green signal. (B) FISH analysis for IGH-CCND1 t(11;14) dual colour dual fusion probe set: each cell nucleus has two red (CCND1) and two green (IGH) FISH signals, one for each copy of the chromosome: this signal pattern indicates the absence of IGH/CCND1 fusion.

Table 1 Antibodies and ZytoLight SPEC Dual Color FISH probes.

Antibody	Clone	Genes	Probe types	Chromosomal regions
PAX5	Clone SP34	CCND1/IGH	Dual fusion	(11;14) (q13.3;q32.3)
CD20	Clone L26	CCND1	Break apart	11q13.3
BCL2	Clone 124	MYC	Break apart	8q24.21
CD10	Clone SP67	BCL2	Break apart	18q21.33
BCL6	Clone GI191E/A8	BCL6	Break apart	3q27.3
IRF4/MUM1	Clone EP190			
CD23	Clone SP23			
CD5	Clone SP19			
Cyclin D1	Clone SP4			
SOX11	Clone MRQ-58			
TdT	Polyclonal			
CD34	Clone QBEnd/10			
c-MYC	Clone Y69			
Ki-67	Clone MiB1			
EBV-encoded RNA	EBER			

Results of all FISH analysis provided by International System for Human Cytogenomic Nomenclature (ISCN) 2016.

concordance is usually present between cyclin D1 positivity and SOX11 expression in mantle cell lymphoma. However, SOX11-negative mantle cell lymphoma does exist,³ so we could not exclude the BVMCL by the absence of SOX11 on the tumour cells. Therefore, the negative results of the FISH analysis for CCND1 gene rearrangement played a key role in excluding BVMCL.

Expression of CD5 and cyclin D1, respectively, has been observed in 5–10% and 1–5% of DLBCL other than MCL.^{4,5} CD5 is typically a marker of aggressive behaviour and poor prognosis for DLBCL. In addition, a small proportion of DLBCLs are also positive for cyclin D1 in a small

number of tumour cells, which may be confused with pleomorphic subtype of MCL, but such DLBCLs usually show no evidence of CCND1 gene translocation.⁶ Concurrent expression of both CD5 and cyclin D1 has never been reported in HGBCL-NOS before and the expression of cyclin D1 in our case of HGBCL-NOS brought BVMCL into the differential diagnosis. In addition, it should not be forgotten that rare cases of MCL carry the rearrangement of the MYC gene as well and typically have aggressive morphological hallmarks such as blastoid or pleomorphic cytology and a dismal prognosis.⁷ We have learned from this case that occasionally these two tumours could be morphologically and

immunophenotypically indistinguishable. To our knowledge, this is the first example of HGBCL-NOS with concurrent expression of CD5 and cyclin D1, strongly mimicking BVMCL. In this setting, only the absence of the *CCND1* gene rearrangement evaluated with both dual fusion and break-apart FISH probes excluded BVMCL and allowed us to classify the neoplasm as HGBCL-NOS.

Unlike DH/TH lymphomas, HGBL-NOS do not carry the gene rearrangements for *c-MYC* and *BCL2* and/or *BCL6*. Moreover, the genetic landscape of HGBL-NOS is not well understood, and few cases carry translocation involving chromosome 8q24 (*MYC*) alone, also called SHL.⁸ Our case harboured a single *c-MYC* rearrangement despite morphological and phenotypic criteria for BL being excluded. This last cytogenetic finding in addition to blastoid morphology, permitted us to place this aggressive lymphoma into the category of HGBCL-NOS despite its own unusual phenotype.

The group of lymphoproliferative disorders such as HGBCL-NOS are recognised as aggressive neoplasms with poor prognosis and short overall survival.¹ Usually, single-hit HGBCL-NOS has a similarly poor prognosis as that of DH/TH lymphomas.⁹ In fact, *MYC* rearrangements predict poor survival in HGBCLs, and as in BL, *MYC* rearrangement could be the driver in HGBCL-NOS. However, very few studies have focused on the prognostic relevance of *MYC* rearrangement in HGBCL-NOS without *BCL2* and/or *BCL6* translocations. Therefore, this issue is an area of controversy.⁹ To date, the impact of CD5 as a prognostic factor in HGBCL-NOS is unknown. Likewise, as to the negative prognostic significance of the presence of CD5 in DLBCL, it might be possible to speculate that the expression CD5 may also serve as an indicator of biological aggressiveness in HGBCL-NOS. Furthermore, we do not have any insight regarding the prognostic role of cyclin D1, keeping in mind that to date there are no published data on the prevalence of cyclin D1 expression in HGBCL-NOS.

In conclusion, this is the first report of HGBCL-NOS with *MYC* rearrangement and concurrent overexpression of CD5 and cyclin D1. Therefore, the present case suggests that occasionally HGBCL-NOS can closely mimic BVMCL both morphologically and phenotypically. Their distinction is especially important clinically, as these two aggressive diseases have quite different treatment strategies. Therefore, a careful molecular work-up for all high-grade B-cell lymphomas with blastoid features is of paramount importance to provide the right diagnosis.

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Concomitant diagnosis of chronic myeloid leukaemia and myeloma

To the Editor,

G-banding for karyotype analysis has been part of routine pathological practice since the 1970s, playing a critical role in improving our understanding of the genetic causes of malignancies. Whilst newer methods, such as fluorescent *in situ* hybridisation (FISH) testing and sequencing technologies have evolved and now play a critical role in diagnosis and management of patients, karyotypic analysis remains an important tool in our diagnostic armament. We present a case which demonstrates the ongoing role that karyotype analysis continues to play and which led to a therapeutic change in management.

A 57-year-old male teacher was referred with an incidental finding of a raised lambda light chains of 597.0 mg/L (reference range 5.7–26.0 mg/L) detected during routine blood testing screening for diabetic nephropathy. His kappa light chains were 9.7 mg/L (reference range 3.3–19.4 mg/L) with a ratio of 0.016 (reference range 0.26–1.65). His past medical history included type 2 diabetes mellitus, hypertension, and benign prostate hypertrophy. He was asymptomatic and examination revealed no lymphadenopathy and no hepatosplenomegaly. He had a normal full blood examination, renal function, and calcium level. Computed tomography (CT) skeletal survey and magnetic resonance imaging (MRI) spine revealed no myelomatous bone disease. He underwent bone marrow aspirate and trephine which demonstrated a