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INDOLENT CLINICAL BEHAVIOUR OF PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE, WITH DOUBLE *MYC* AND *BCL6* GENE REARRANGEMENT.

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Ethics Statement: Informed written consent has been obtained. Studies have been performed according to the Declaration of Helsinki. The procedures have been approved by a local ethics committee. Date 08-11-2018; Approval Number:PICO75-18_FJD; CEIm-FJD.

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Letter

Sir,

In 2010, an 83-year-old woman presented with a 5-cm nodule on her right knee, diagnosed of primary cutaneous-diffuse-large-B-cell lymphomas-leg type (PCDLBCL-LT) that suffered complete remission (CR) after R-CHOP (6 cycles). Eight years later three small nodules at the same site took place (Figures 1A, 2A). Again, after surgery, chemotherapy (R-mini-CHOPx3) and local radiotherapy, CR was achieved without evidence of recurrence two years later. This clinical behaviour is surprising since the prognosis of most PCDLBCL-LT patients is usually poor, with multiple cutaneous-extracutaneous recurrences (Willemze *et al,* 2019). Notwithstanding, spontaneous regression of some cases has been reported (Graham *et al*, 2018).

Histologically, the 2010 cutaneous-biopsy consisted of a dermis-subcutaneous tissue diffusely infiltrated by medium-sized round cells with scant cytoplasm, hyperchromatic nuclei and small nucleoli (Figure 1). Apoptotic cells and mitotic figures were found. In contrast, the 2018 lesion showed larger cells with abundant cytoplasm, round nuclei and rather prominent nucleoli (Figure 2). Epidermis was spared in both specimens. The immunophenotype of both samples was identical, showing neoplastic cells CD20, BCL6, CD10, BCL2 and MYC and were negative for CD30, Cyclin D1, SOX11, TdT, MUM1, p53 and EBV (EBER) (Figures 1, 2). The proliferation activity (Ki-67) was high (almost 100%). Based on morphology and immunophenotype the diagnosis of DLBCL of GC-phenotype (according to Hans-algorithm) was made in both instances.

Given the double expression of MYC and BCL2, fluorescent in situ hybridization (FISH) studies for *BCL6*/*BCL2* and *MYC* genes were performed. Translocations of both *MYC*/*BCL6* genes were found. Interestingly, a biallelic and a monoallelic *MYC* gene rearrangement was detected in the first and second biopsy, respectively (Supplementary Figure 1). To the best of our knowledge this finding has not been described so far in PCDLBCL-LT or systemic high-grade B cell lymphomas with *MYC*/*BCL2/BCL6* rearrangements (HGBCL-DH/TH), although it has been reported for *DUSP22* gene in anaplastic large cell lymphomas (Csikesz *et al*, 2013).

NGS studies identified a *BCL6*-IGL rearrangement, with identical breakpoints on *BCL6* and *IGLJ1* in both samples. Rearrangements of *BCL6* to *IGL* or to other *non-IG partners* probably have an influence on prognosis (Ueda *et al*, 2002). Interestingly, a

MYC-IGH translocation was identified in the 2010 sample but not at relapse. Moreover, a fusion (using a fusion *MYC*-IGH probe) was identified at first diagnosis, but not at relapse, confirming NGS results (Supplementary Figure 2). It is well known that the majority of *MYC* rearrangements in HGBL-DH/TH have non-*IG* partners (Chong *et al*, 2018).

HGBL-DH/TH are usually of GC phenotype (Ennishi *et al*, 2017) while PCDLBCL-LT are typically of ABC phenotype. 16% of PCDLBCL-LT show CD10 expression, inversely correlated to the presence of *MYC* gene translocation (Schrader *et al*, 2018). Over 90% of cases of PCDLBCL-LT express BCL2, and about two thirds of them are double expressors. Furthermore, *MYC* rearrangement has been reported in 32% of the cases (Willemze *et al*, 2019), with only two cases described so far of double rearrangement (Schrader *et al*, 2018). Both double expression of BCL2/MYC or *MYC* gene rearrangement in PCDLBCL-LT patients are related to poor outcome (Schrader *et al*, 2018). The presence of a second hit involving *BCL6* gene did not seem to make any difference in cases with *MYC* gene rearrangements (Schrader *et al*, 2018). Prognosis of HGBL-DH/TH depends not only on the partner of *MYC* gene rearrangements but also on whether *BCL2* or *BCL6* gene is the second hit (Rosenwald *et al*, 2019).

NGS also showed the same rearrangements of *IGH* and *IGK* genes (IGHJ4-IGHD3-22, IGKJ2-IGKV1-39, intronRSS-Kde and IGLJ1-IGLV3-21) in both samples although differed in their somatic mutation repertoire. Mutations of *SMARCA4* and *KMT2D* gene were detected in the first biopsy but not in the second one, while *FAT1* gene mutation appeared only in the recurrence. The remaining gene alterations (*CD79B, TNFAIP3, HIST1H1E* and *PIM1*) were present in both (Supplementary Table 3).

MYD88 p.L265P mutation, present in about 60% of PCDLBCL-LT cases, and related to poor prognosis (Mareschal *et al*, 2017) was not found here, neither by Q-PCR nor NGS. Other genes previously reported in PCDLBCL-LT were present both in the first biopsy and at relapse (*CD79B, HIST1H1E* and *PIM1*) (Mareschal *et al*, 2017). Mutations on the *TNFAIP3 (A20)* gene has not been previously reported in PCDLBCL-LT, even though deletions of this gene are frequent (Mareschal *et al*, 2017). Interestingly, in the first biopsy, mutation of genes related to germinal centre B-cell origin lymphomas, such as *SMARCA4* or *KMT2D (MLL2)* were found. Significance of mutations in *FAT1* is still not known in DLBCLs. Interestingly, biallelic *CDKN2A* gene deletions were identified in both samples.

These data imply that the lymphoma diagnosed in 2018 was a *bona fide* recurrence of the one diagnosed in 2010, demonstrating that both tumours share a common clonal progenitor but were subjected to divergent evolution (Supplementary Figure 3).

PCDLBCL-LT are aggressive lymphomas characterized by a proliferation of immunoblastic-like large neoplastic B cells of ABC-phenotype which characteristically show both *MYD88 p.L265P* mutations and *CDKN2A* gene deletions. Secondary skin involvement by a systemic HGBL-DH/TH, Burkitt lymphoma, mantle cell lymphoma and systemic follicular lymphoma transforming into HGBL-DH/TH could be ruled out both clinically and immunophenotypically. Nevertheless, primary cutaneous follicular lymphoma (PCFCL) with a diffuse pattern and predominance of large cells should be taken into consideration. These usually occur in the head and neck or the trunk. Histologically, a mixture of centrocytes and centroblasts with large amount of small bystander T-cells and scattered CD23 or CD21-positive residual follicular dendritic cells is seen. They are characteristically BCL2 and CD10 negative. BCL2 positive cases with CD10 expression and *BCL2* gene translocation, makes it advisable to rule out a systemic origin. Only mutations in the TNFRSF14 gene have been reported in PCFCL, usually in combination with 1p36 deletion (Gángó *et al*, 2018). All these facts together allowed us to exclude the diagnosis of PCFCL with a diffuse pattern.

In conclusion, we report a PCDLBCL-LT that showed peculiar immunophenotype, molecular background, and a remarkably indolent clinical behaviour. These data suggest that the group of PCDLBCL-LT is more heterogeneous than previously thought.

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Figure Legends:

Figure 1. Tumour diagnosed in 2010. (A). Large nodule on the anterior aspect of the right knee of an 83-year-old woman. (B) Panoramic view showing diffuse involvement of dermis and subcutis on histopathologic study (H-E stain, 2X) (C). Sheets of large atypical cells (H-E stain x 20). Neoplastic cells showing expression of CD10 (20X) (D), BCL2 (20X) (E), MYC (20X) (F) and a high proliferation index with KI67 (20X) (G).

Figure 2. Recurrence of the lesion in 2018, as three small nodules on the site of the previous lesion (A). Extensive involvement of the dermis (H-E stain, 4X) (B). Detail of the morphology of neoplastic cells (C) (20X). Neoplastic cells expressed CD20 (D) (4x), and CD10 (E) (4X), were negative for MUM1 (F)(4x) and showed a high proliferation index with KI67 (G)(4x).