V SIMPOSIUM DEL GRUPO DE ESTUDIO LATINOAMERICANO DE **LINFOPROLIFERATIVOS**

COMITÉ ORGANIZADOR: JUNTA DIRECTIVA GELL 2021 -2023

GELL
Grupo de Estudio Latinoamericano de Linfoproliferativos

Linfoma B difuso de células grandes primario de la piel, tipo de la pierna: regresión espontánea

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No conflicts of interest to disclose

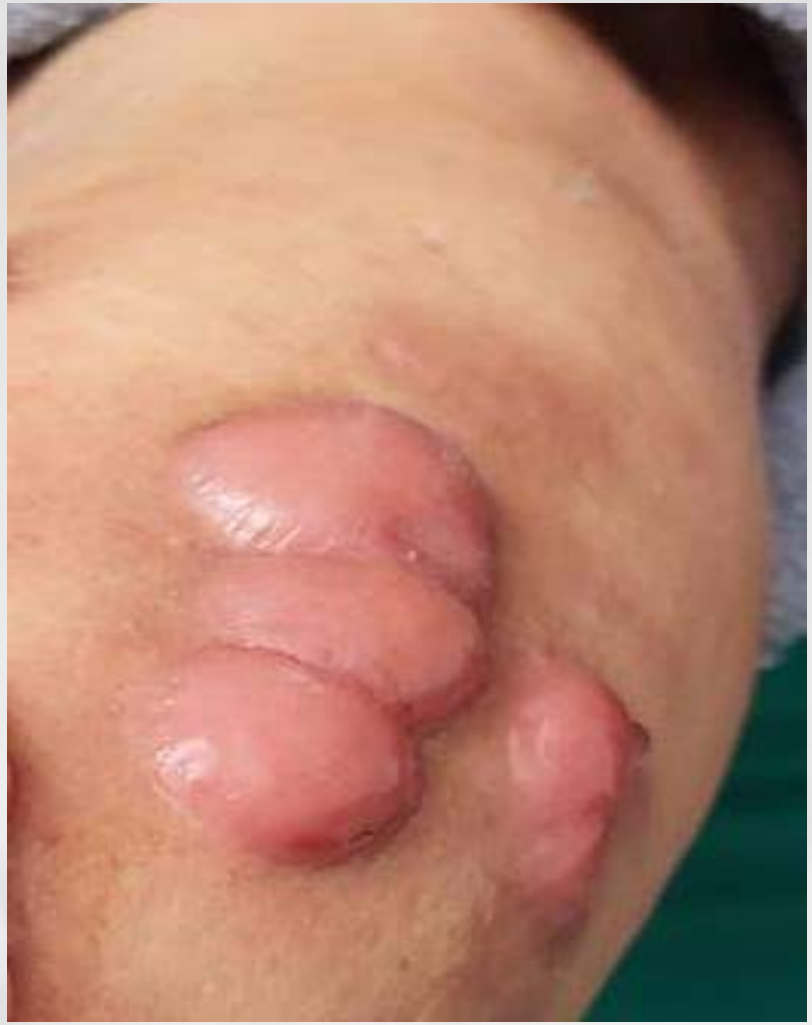
Member of NCCN Panel for Primary cutaneous T and B cell lymphomas

Case

- A previously healthy 73-year-old man was referred to the Oncology Department, Hospital Nacional Edgardo Rebagliati, Lima, complaining of five painless nodules on his right leg for the last three months.
- The lesions started as small red papules, which rapidly increased in size.
- The patient denied any fevers, pain, pruritus, or other systemic symptoms.

Case

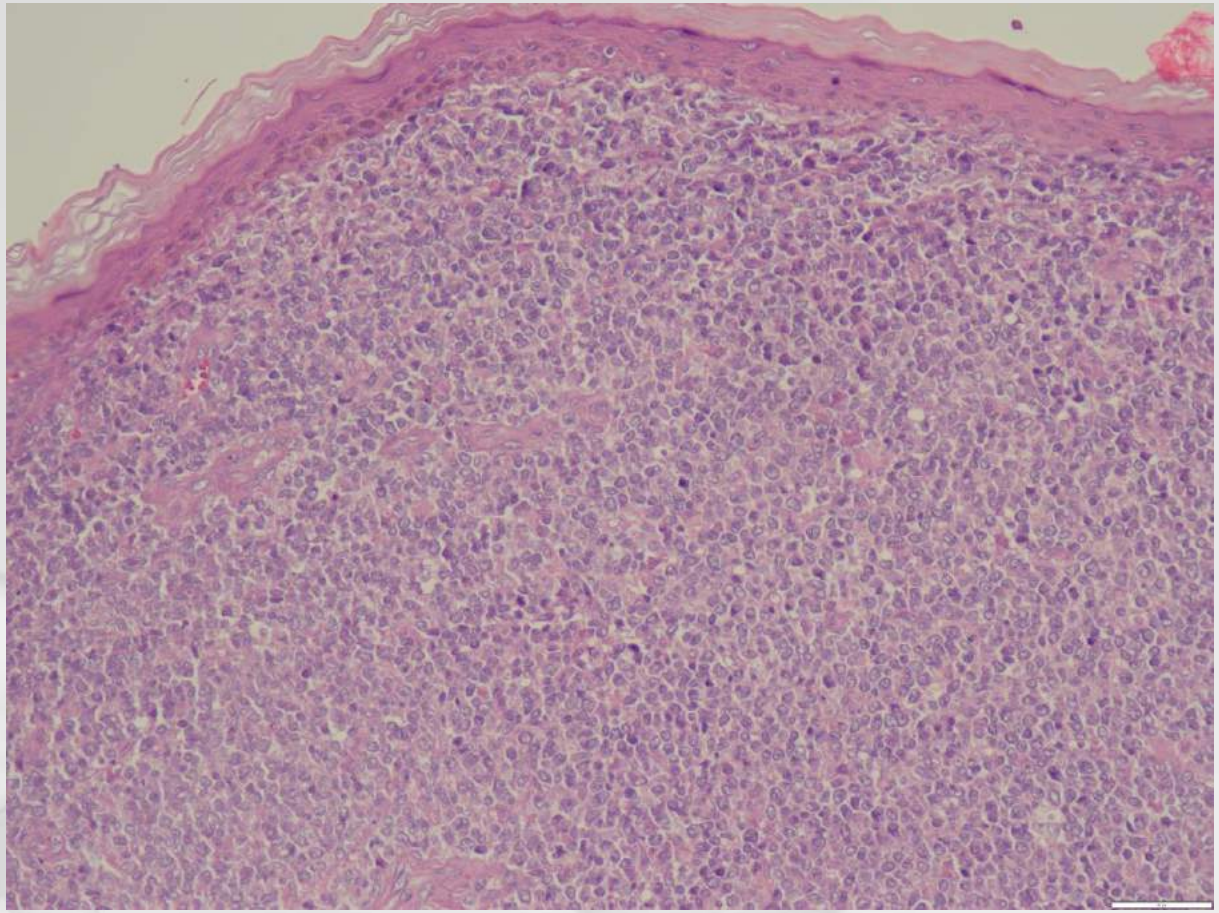
- Physical examination revealed three erythematous, indurated nodules measuring 3cm in diameter in aggregate, located on the posteromedial side of his right leg
- No lymphadenopathy was present.

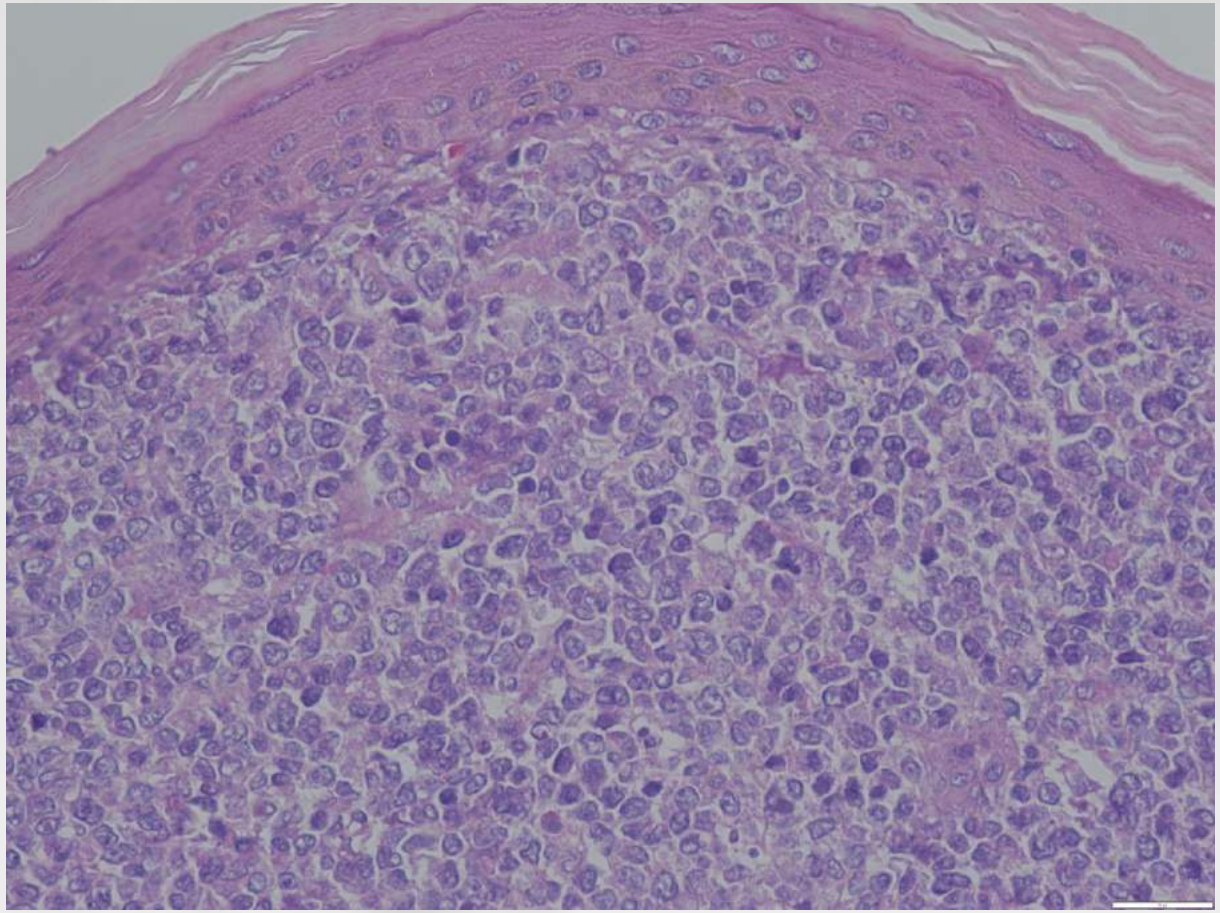


Courtesy of Brady Beltrán MD

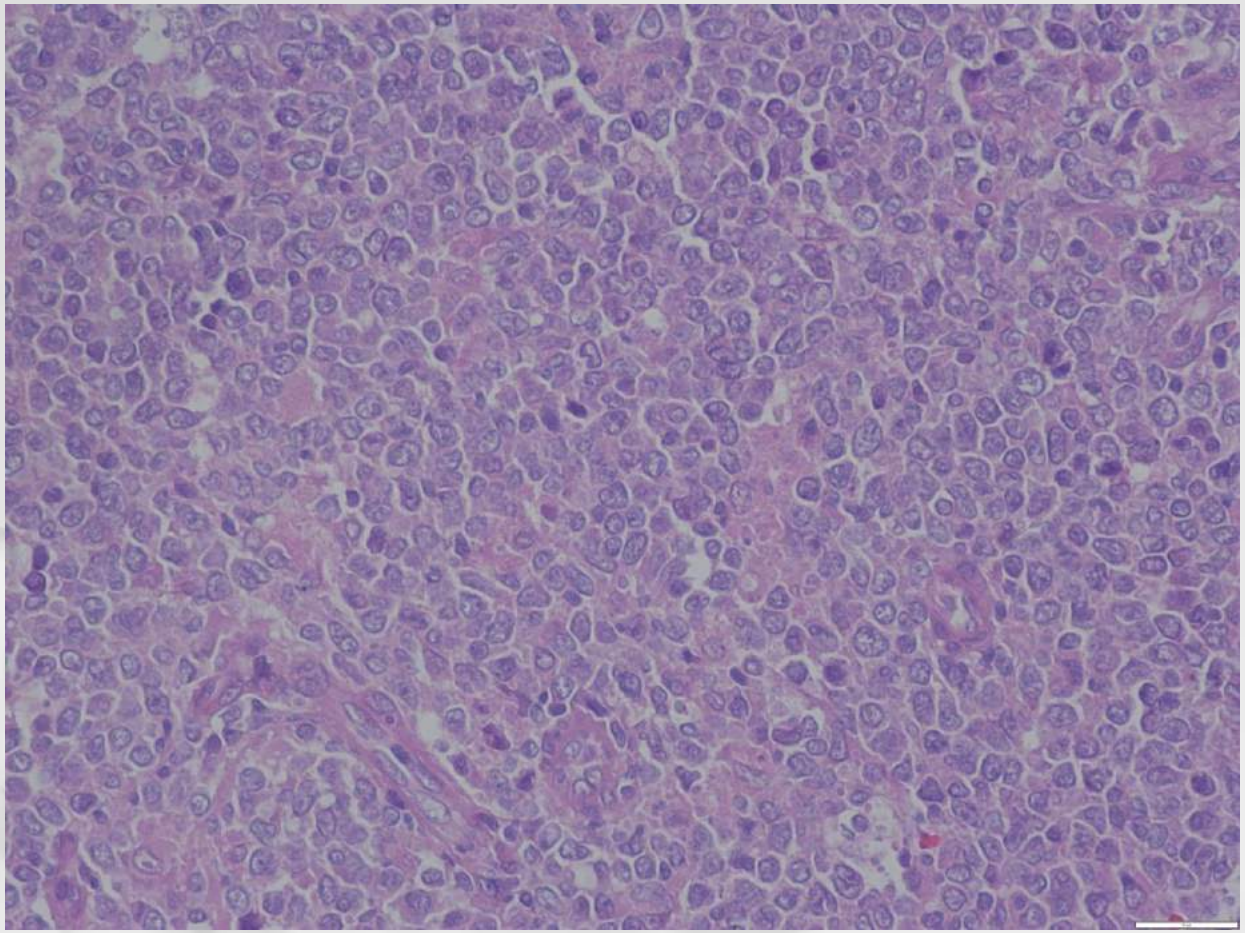
Case

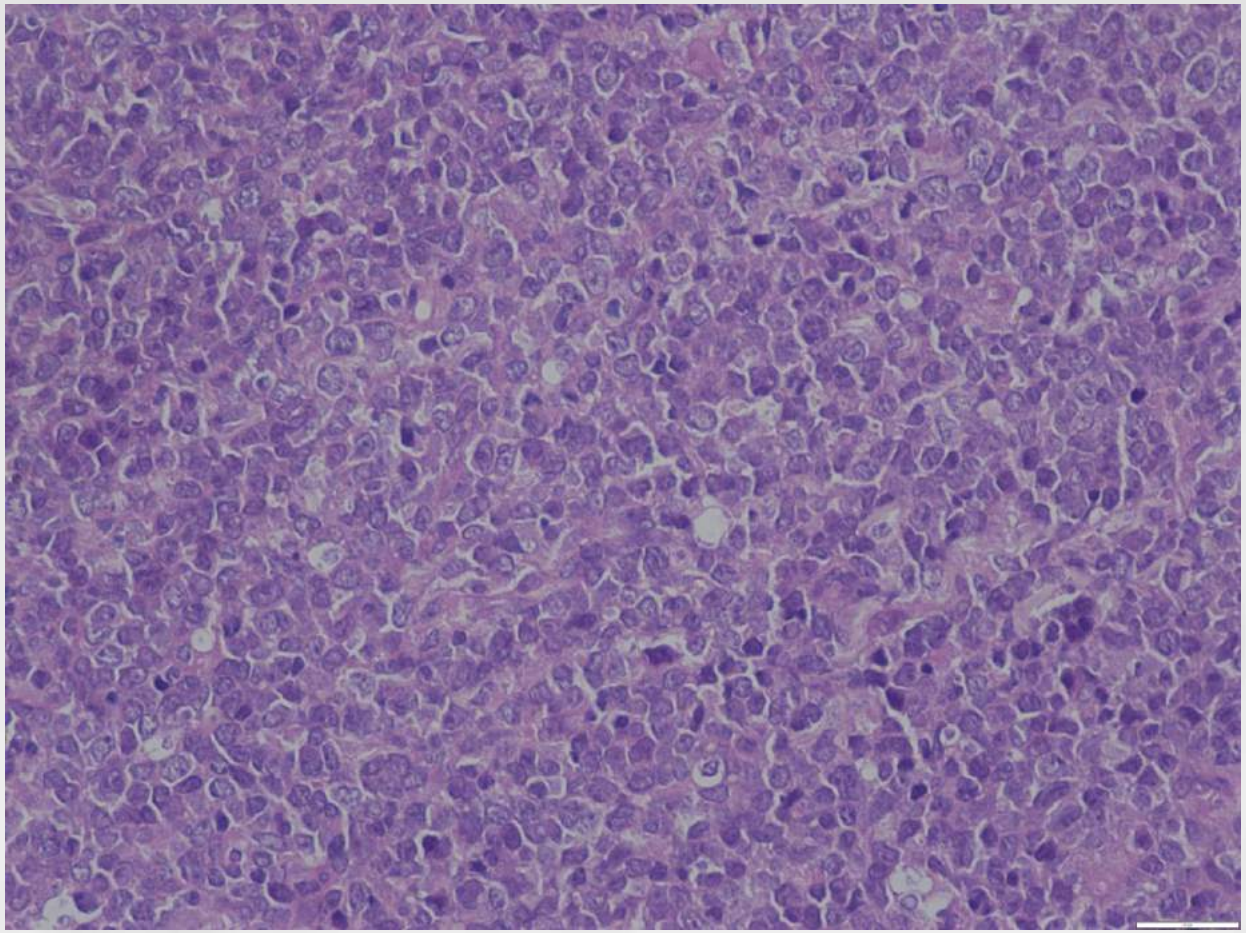
- Laboratory work up including serum lactate dehydrogenase, coagulation profile, autoantibodies, protein electrophoresis, HTLV- 1, HIV, hepatitis B virus, hepatitis C virus, Epstein-Barr virus were all normal/negative.
- Thorax, abdomen and pelvic CT scan was within normal limits.
- A skin biopsy was performed.





Courtesy of Pilar Quiñones MD





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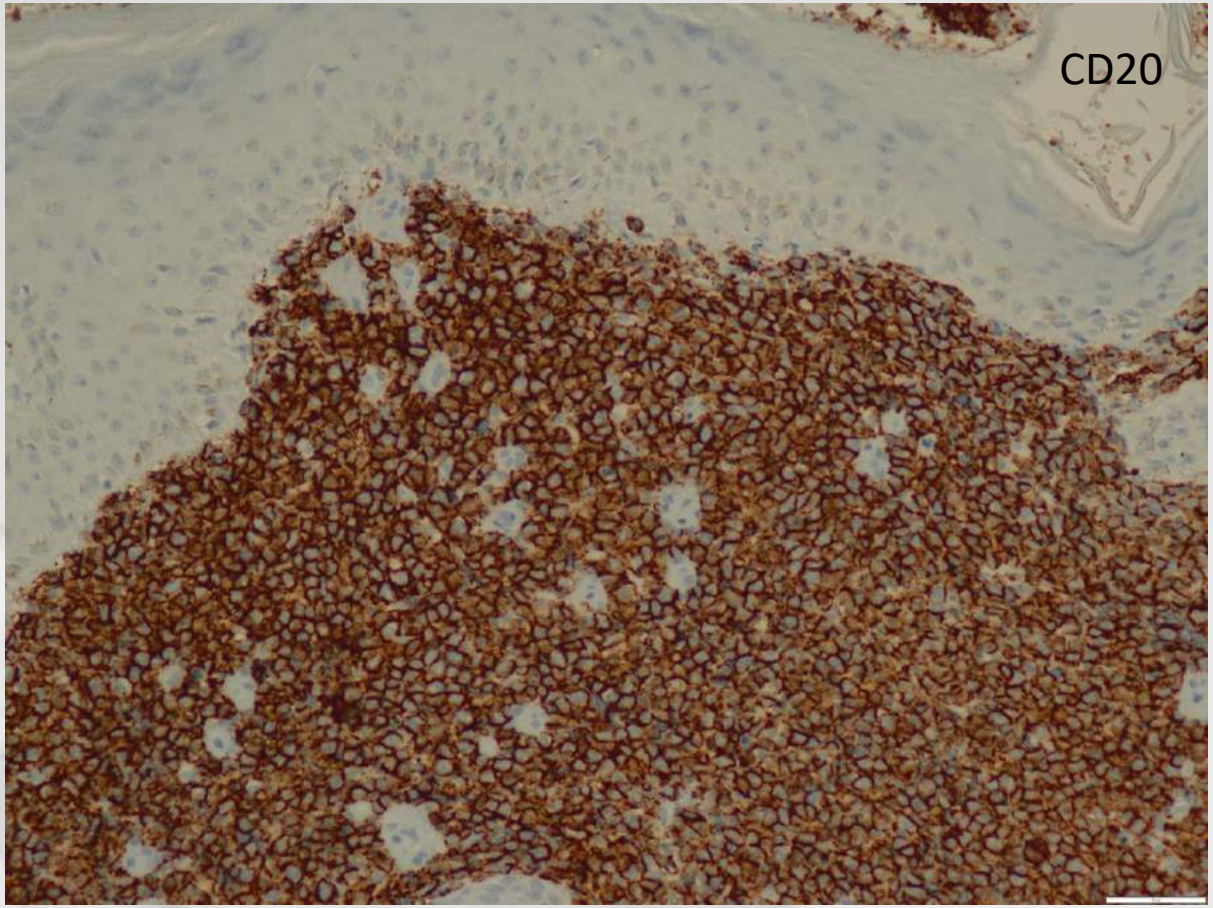

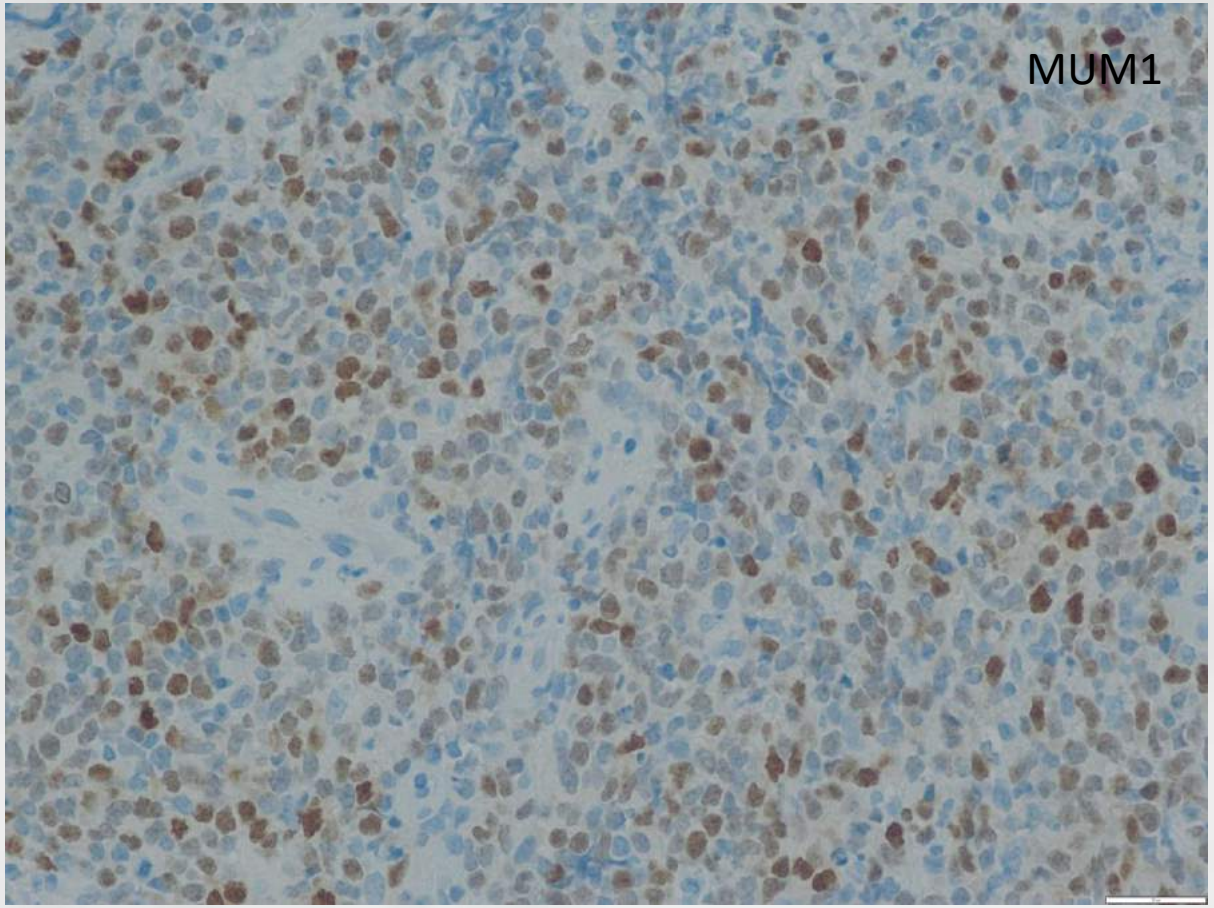

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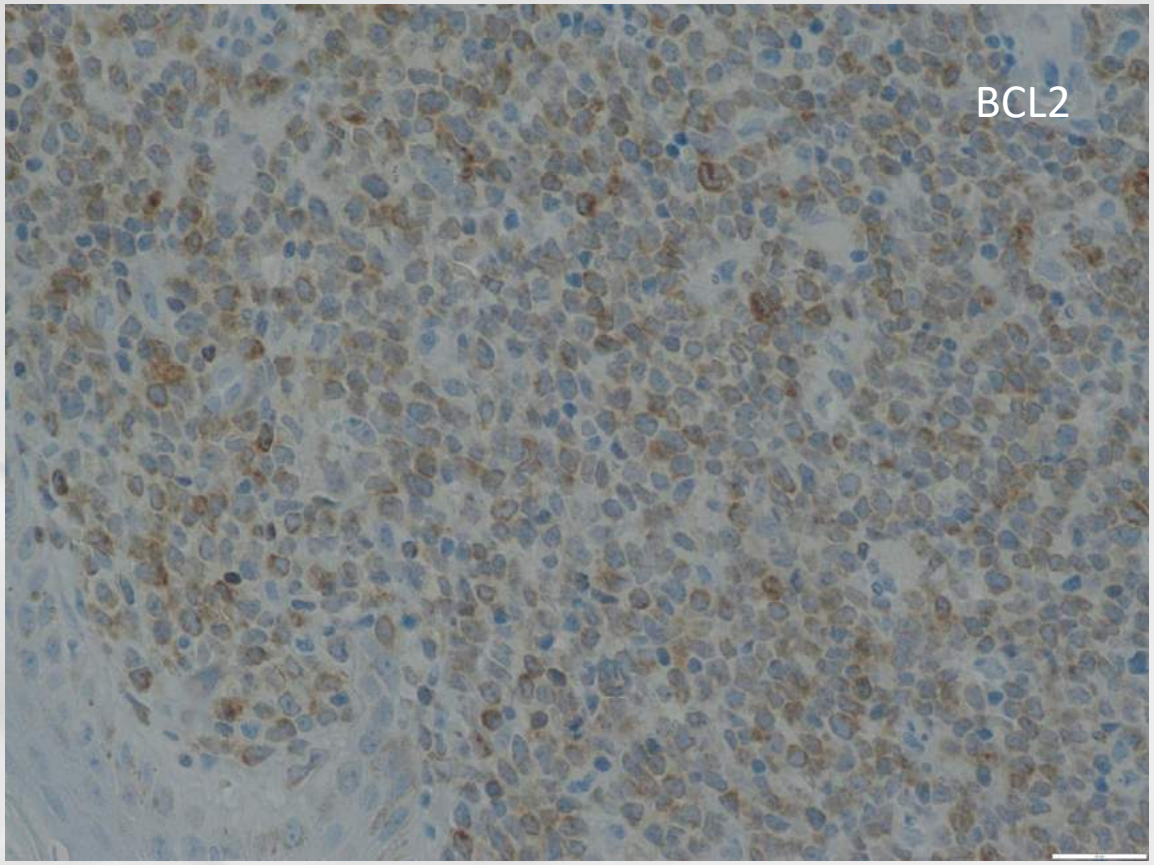

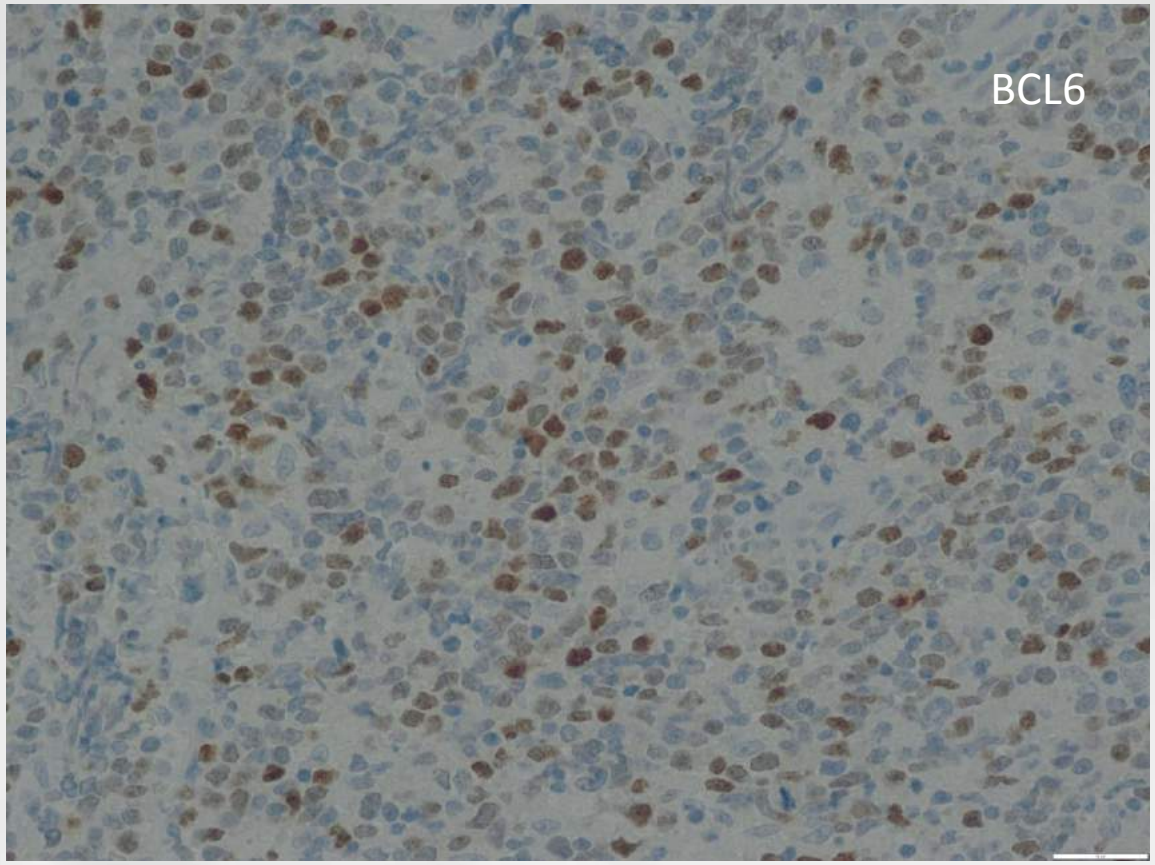

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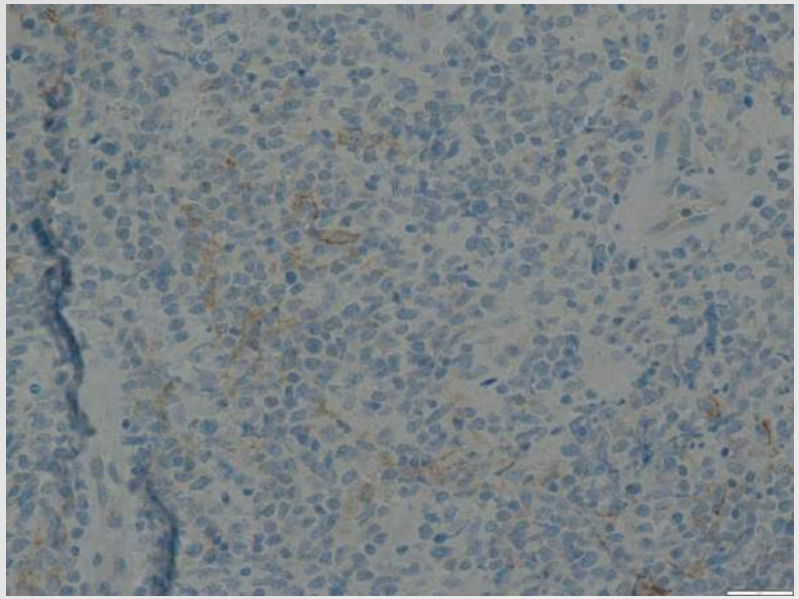
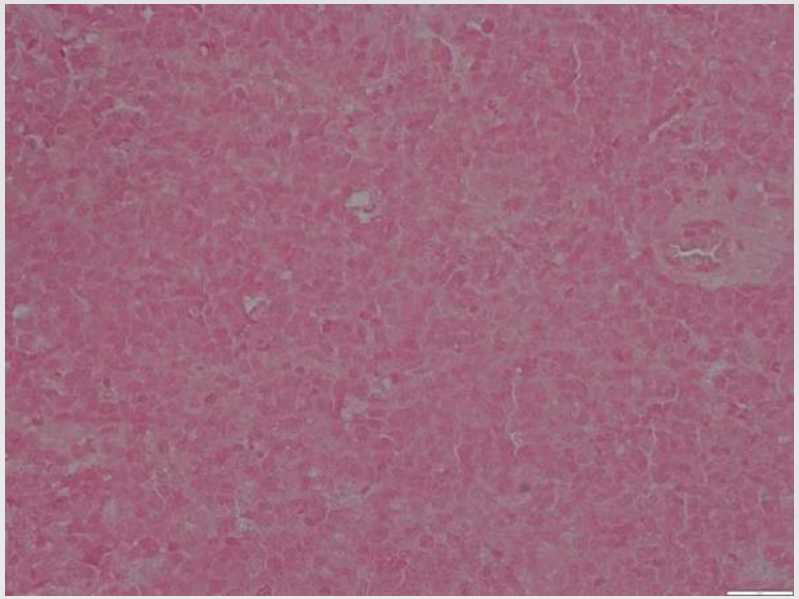
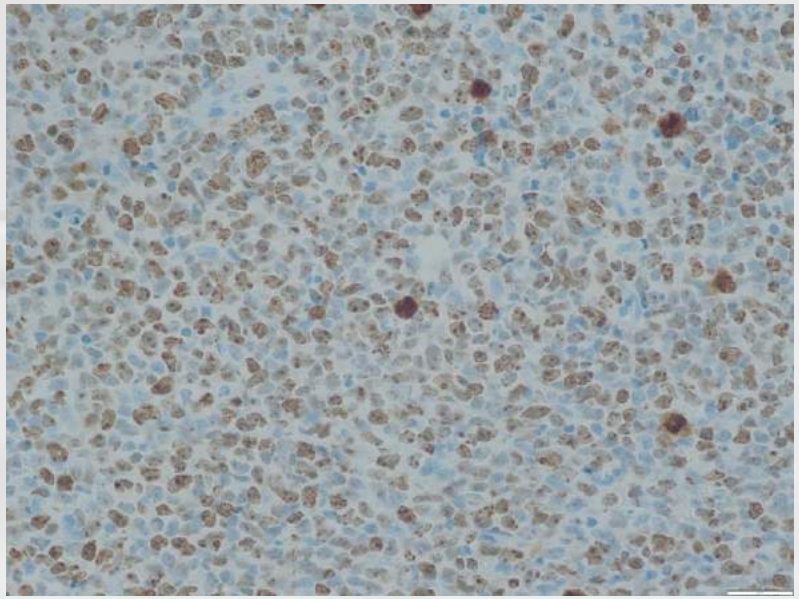
CD10



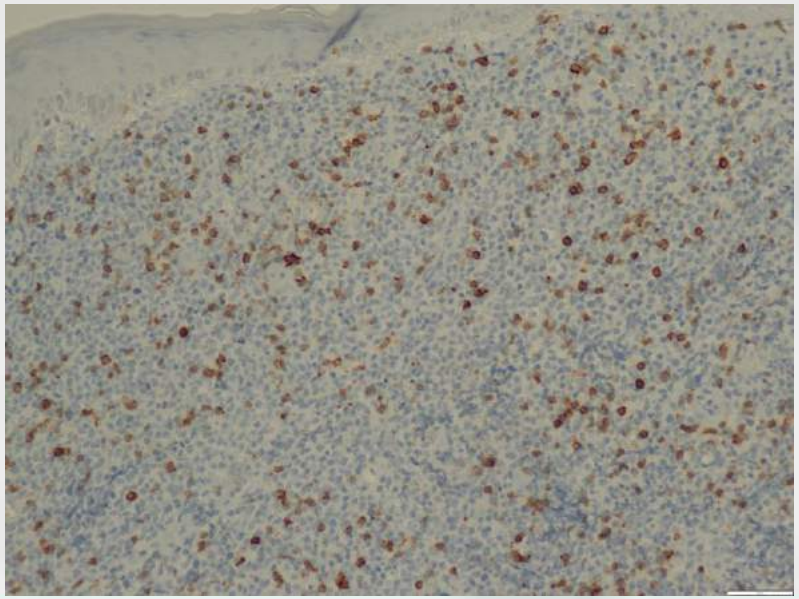
EBER



Ki67



CD5



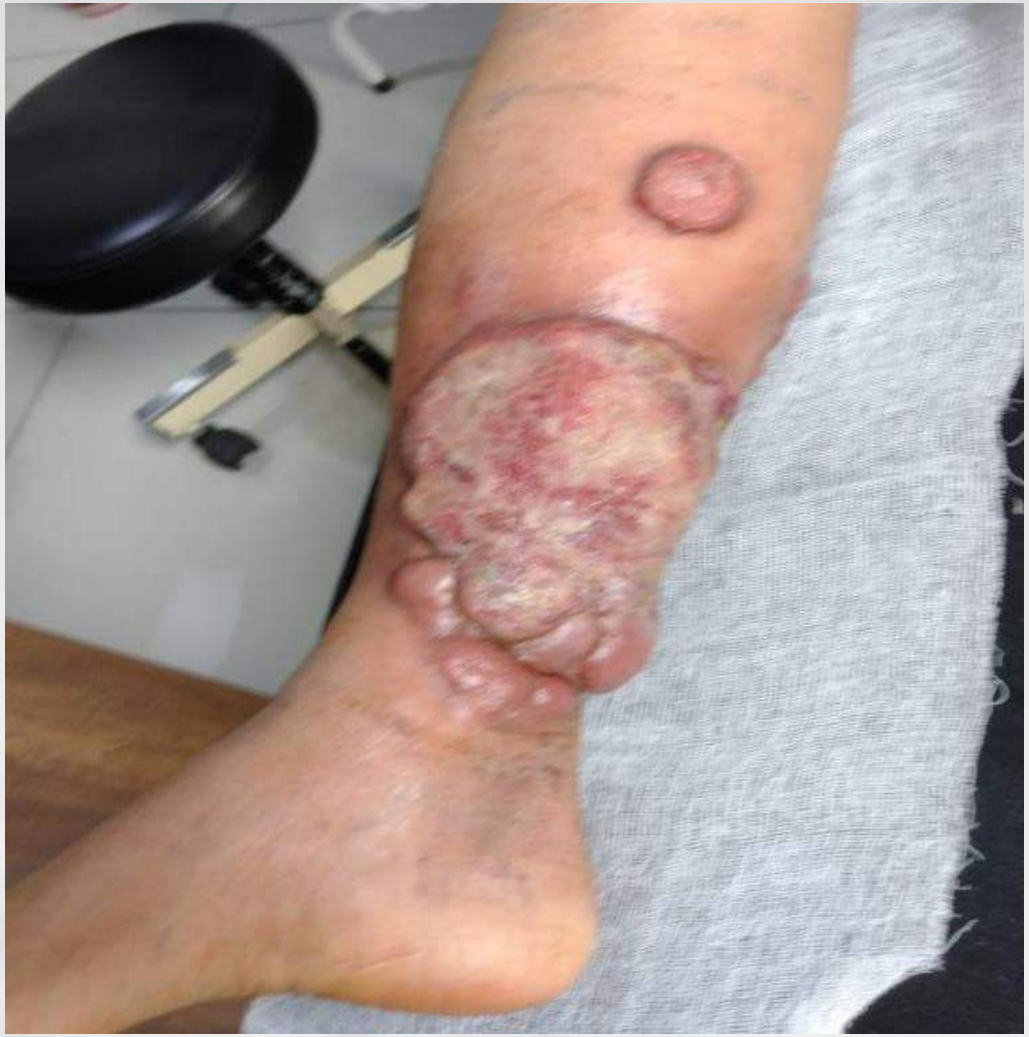
Courtesy of Pilar Quiñones MD

Case

- Diagnosis: primary cutaneous diffuse large B-cell lymphoma, leg type
- The patient refused to undergo any treatment because his skin lesions began to regress spontaneously after the biopsy
- At 5 months from diagnosis, the tumors had undergone complete resolution.
- The patient remained free of clinical disease for 72 months

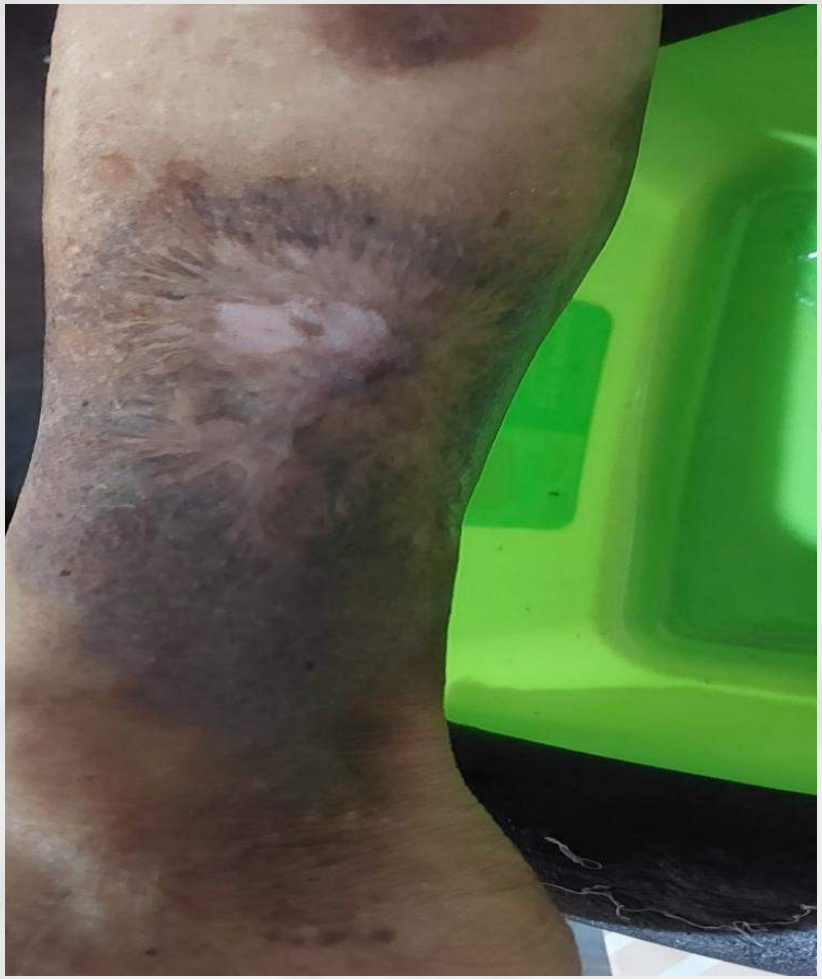
Case

- At the beginning of the sixth year after diagnosis the patient noticed six purple nodules with large areas of ulceration on the anterior aspect of his right leg, measuring 20 x 20 cm in aggregate



Case

- Laboratory workup was within normal limits
- Chest/abdomen/pelvis CT scan was negative
- Patient was treated with R-miniCHOP for 6 cycles with complete response
- The patient is scheduled for radiation therapy for consolidation

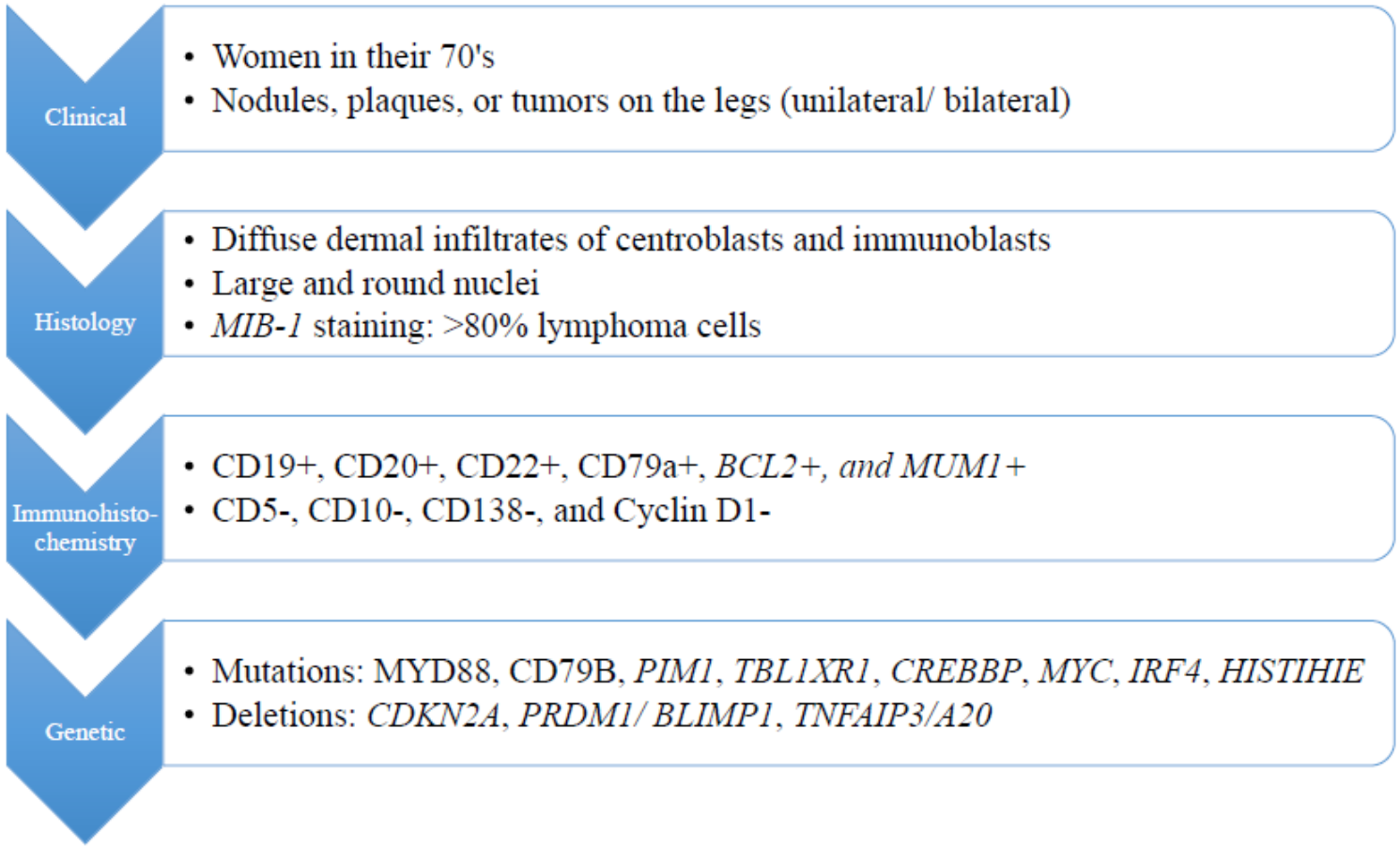


Discussion

- PCDLBL-LT accounts for ~11% of all CBCL and is less frequent than secondary cutaneous DLBCL (7-10% of patients with systemic DLBCL)
- 5-year DSS is 56-66%
- Brownish, reddish, bluish solitary or confluent rapidly growing papules, plaques, or nodules
- Location: Legs (28.7%), scalp and neck (22.2%), face (21.6%) (Blanchard et al, It J Derm and Ven 2023)
- Extracutaneous spread: 10%

Primary cutaneous diffuse large B cell lymphoma, leg type

- Elderly, more commonly women, on legs (not exclusively)
- Non-germinal center phenotype: MUM1+, BCL2+, BCL6+/-, CD10-, IgM+, reports of non-ABC type
- It can be positive for *MYC* rearrangements by FISH (also for *BCL6*, rarely, not for *BCL2*)
- Mutations in *MYD88*^{L265P} and *CD79B* overlap with others such as primary CNS, testicular DLBCL, intravascular large B cell lymphoma, but differ from nodal DLBCL

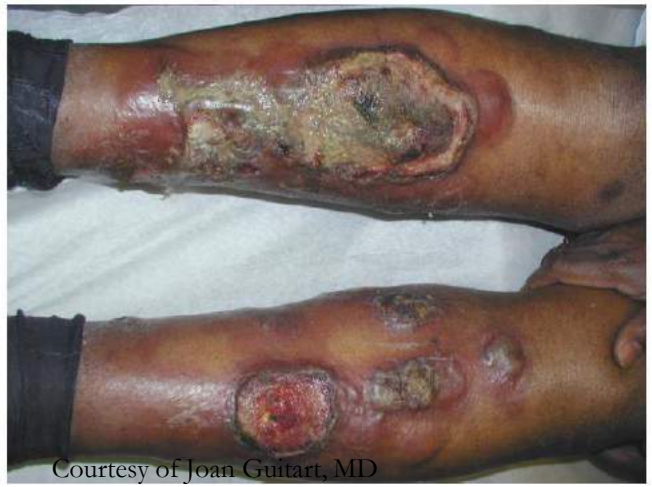


Journal of Investigative Dermatology (2017) **137**, 1831–1833

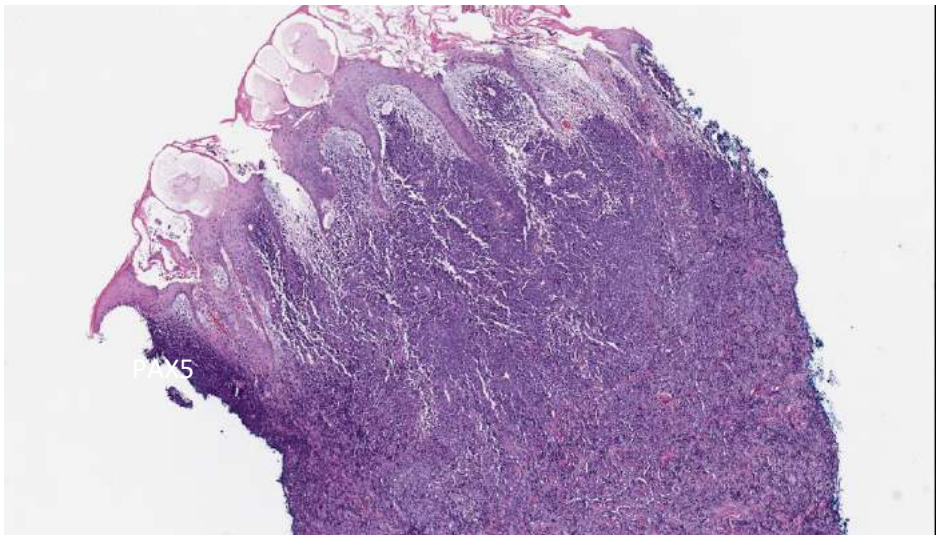
Novel Mutations Involving NF-κB and B-Cell Signaling Pathways in Primary Cutaneous Large B-Cell Lymphoma, Leg-Type and Comparison with Sézary Syndrome

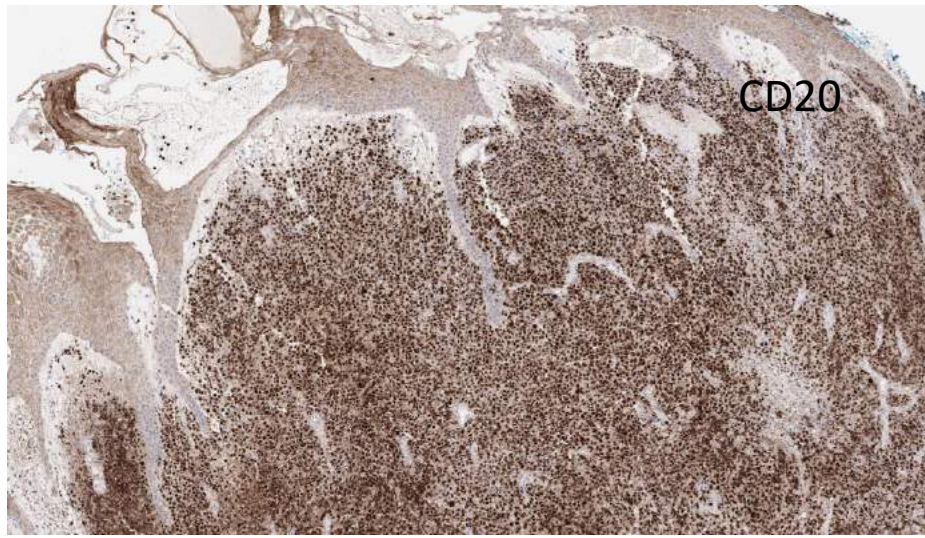
Esther J. Kim[1,2], Daniel J. Lewis[1,2] and Madeleine Duvic[1]

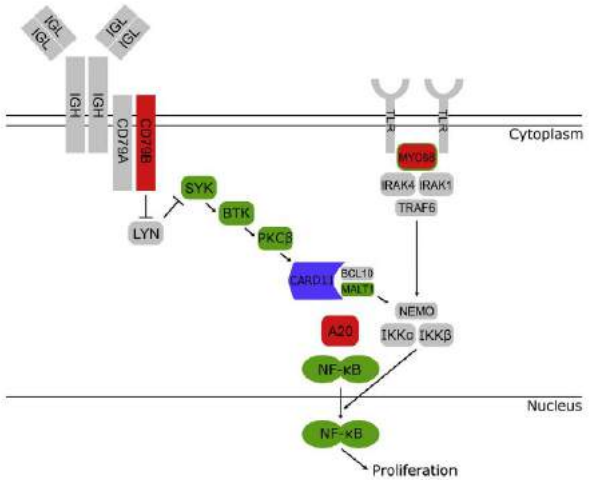
15-20% bilateral or at other skin site (worse prognosis)

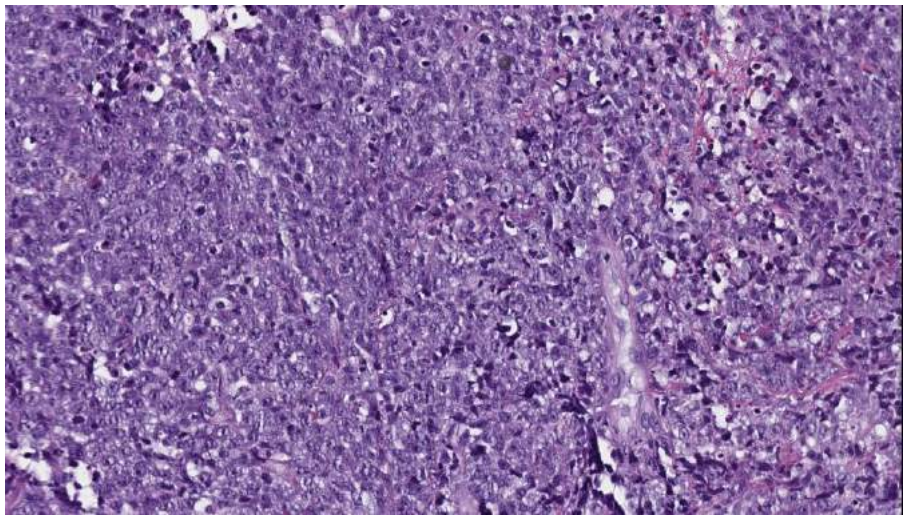


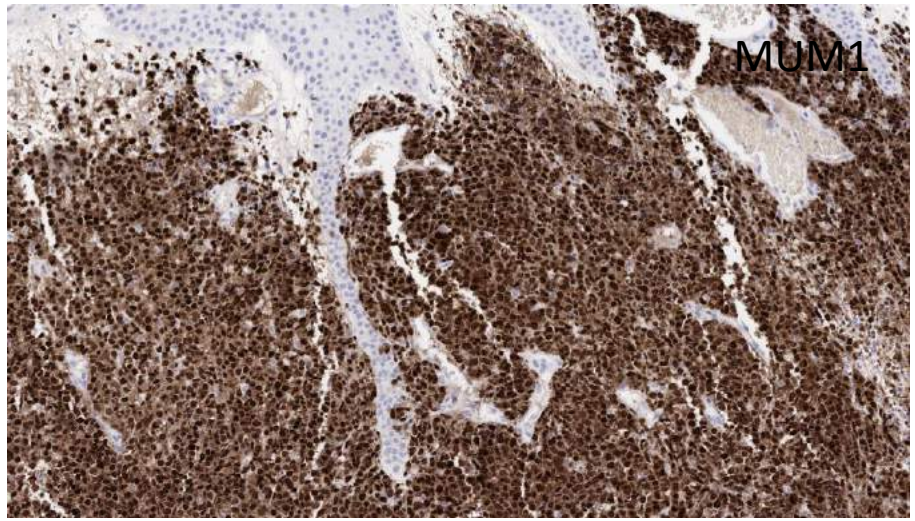
Courtesy of Joan Guitart, MD











Novel Mutations Involving NF-κB and B-Cell Signaling Pathways in Primary Cutaneous Large B-Cell Lymphoma, Leg-Type and Comparison with Sézary Syndrome

Esther J. Kim[1,2], Daniel J. Lewis[1,2] and Madeleine Duvic[1]

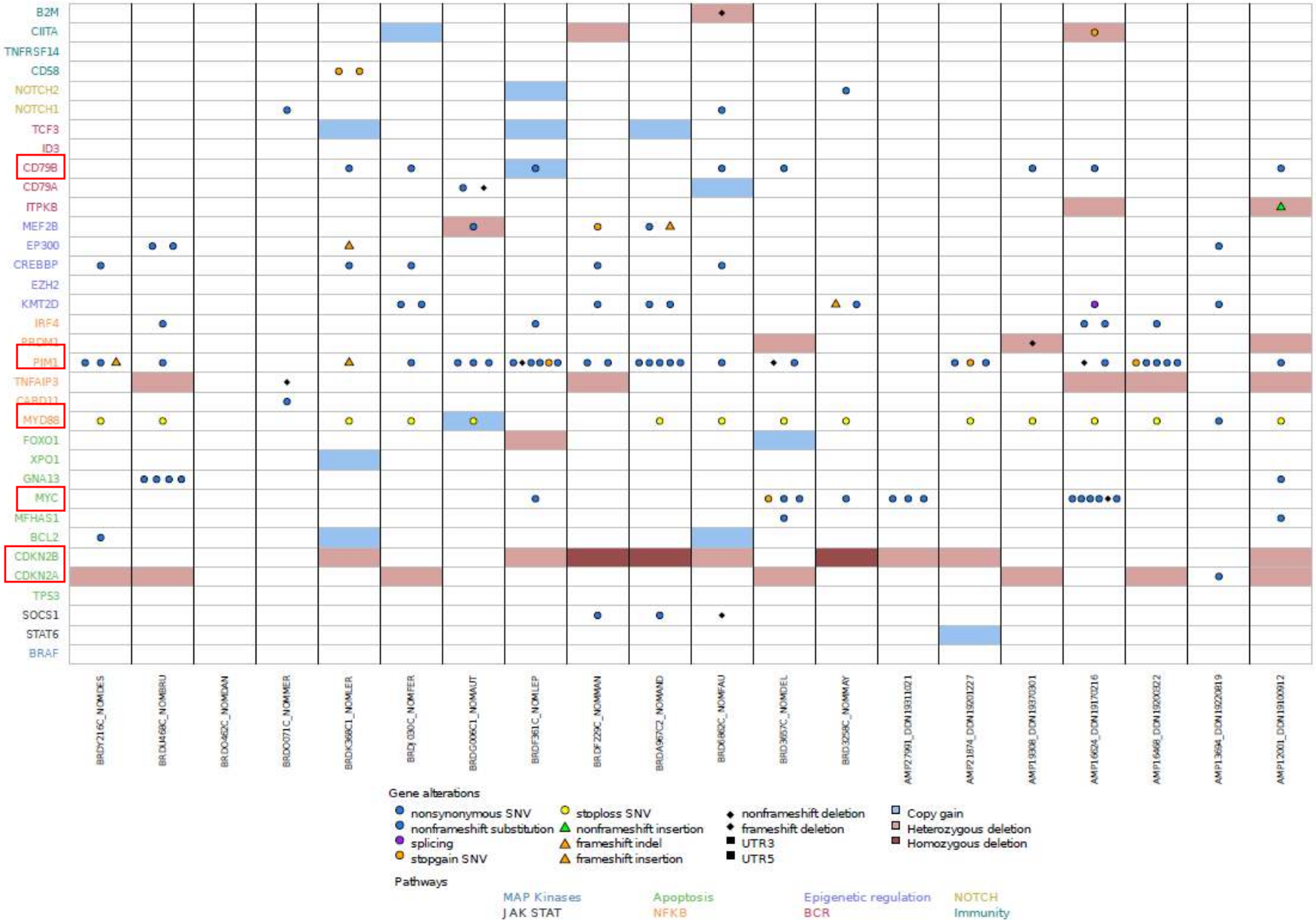
Journal of Investigative Dermatology (2017) **137**, 1831–1833

Primary cutaneous diffuse large B cell lymphoma, leg type

- MYC is positive in 65-80% of cases, in contrast to PCFCL
- *MYC* and *BCL2* translocations (double hit) is <20%
- *MYC* rearrangements and *HIST1H1E* mutations associated with worse outcome
- Inactivation of *CDKN2A* (67%) associated with worse prognosis
- Mutations in BCR pathway (*CD79A/B* or *CARD11*) associated with therapeutic resistance

Primary cutaneous diffuse large B cell lymphoma, leg type

- Genetic landscape somewhat similar to ABC-DLBCL
- NF-κB-activating mutations in *MYD88, PIM1, CD79B*, and *IRF4* (Mareschal, JID 2017)
- *MYD88* L265P mutations are the most common (75%, Menguy, JID 2016)
- Other common mutations are: *MYC, CREBBP, MEF2B, SOCS1* (Mareschal, JID 2017)
- Most frequent copy number variation is 9p21 deletion (75%, most heterozygous)



S Mareschal et al.
Massive Parallel Sequencing in PCLBCL-LT
Journal of Investigative Dermatology (2017), Volume 137

Primary cutaneous diffuse large B cell lymphoma, leg type

- Other *MYD88* non-L265P mutations are rare, in contrast to nodal DLBL, and similar to Waldestrom macroglobulinemia and primary CNS lymphoma (Mareschal et al 2017)
- Sezary syndrome also shows activation of the NF-κB pathway (similar frequent mutations in *TNFAIP3* although higher mutations *CARD11)*

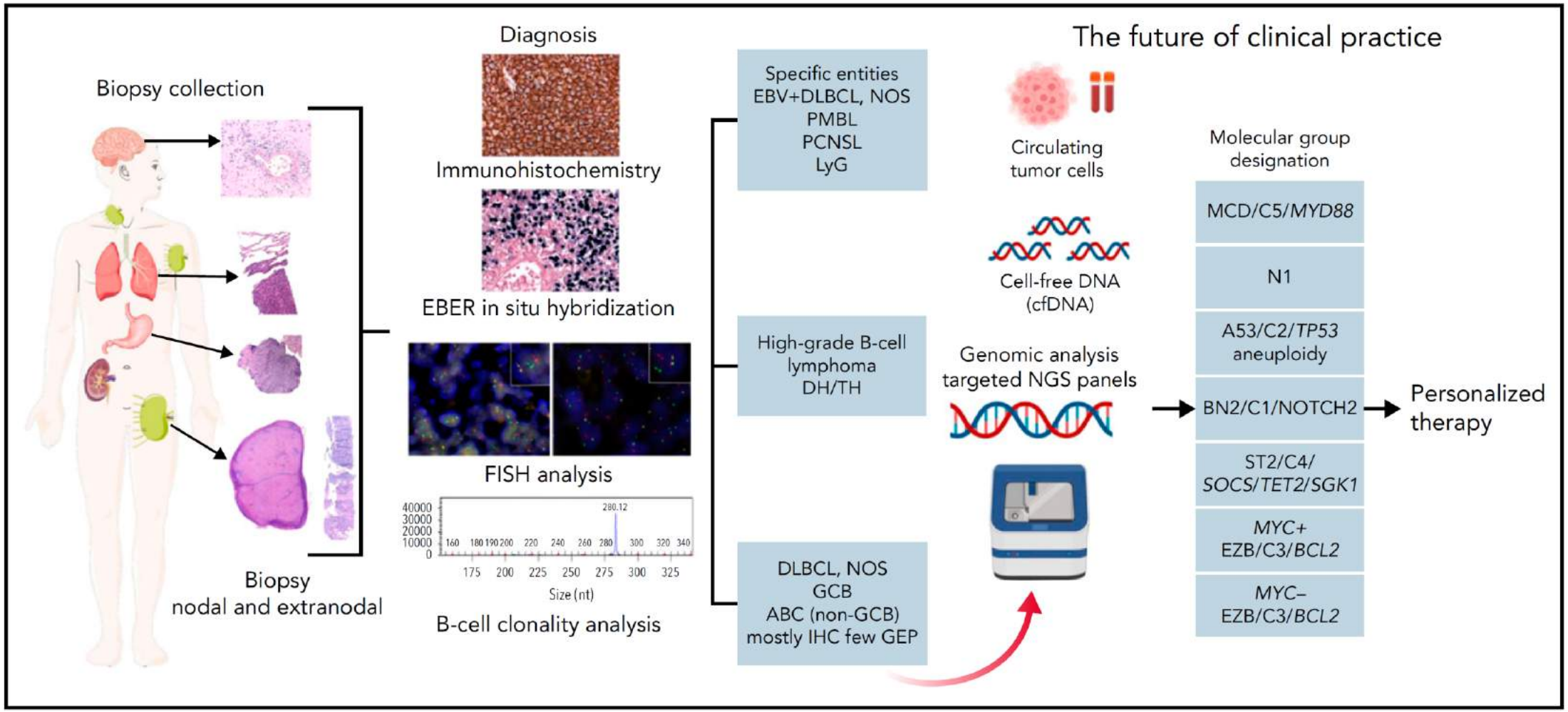
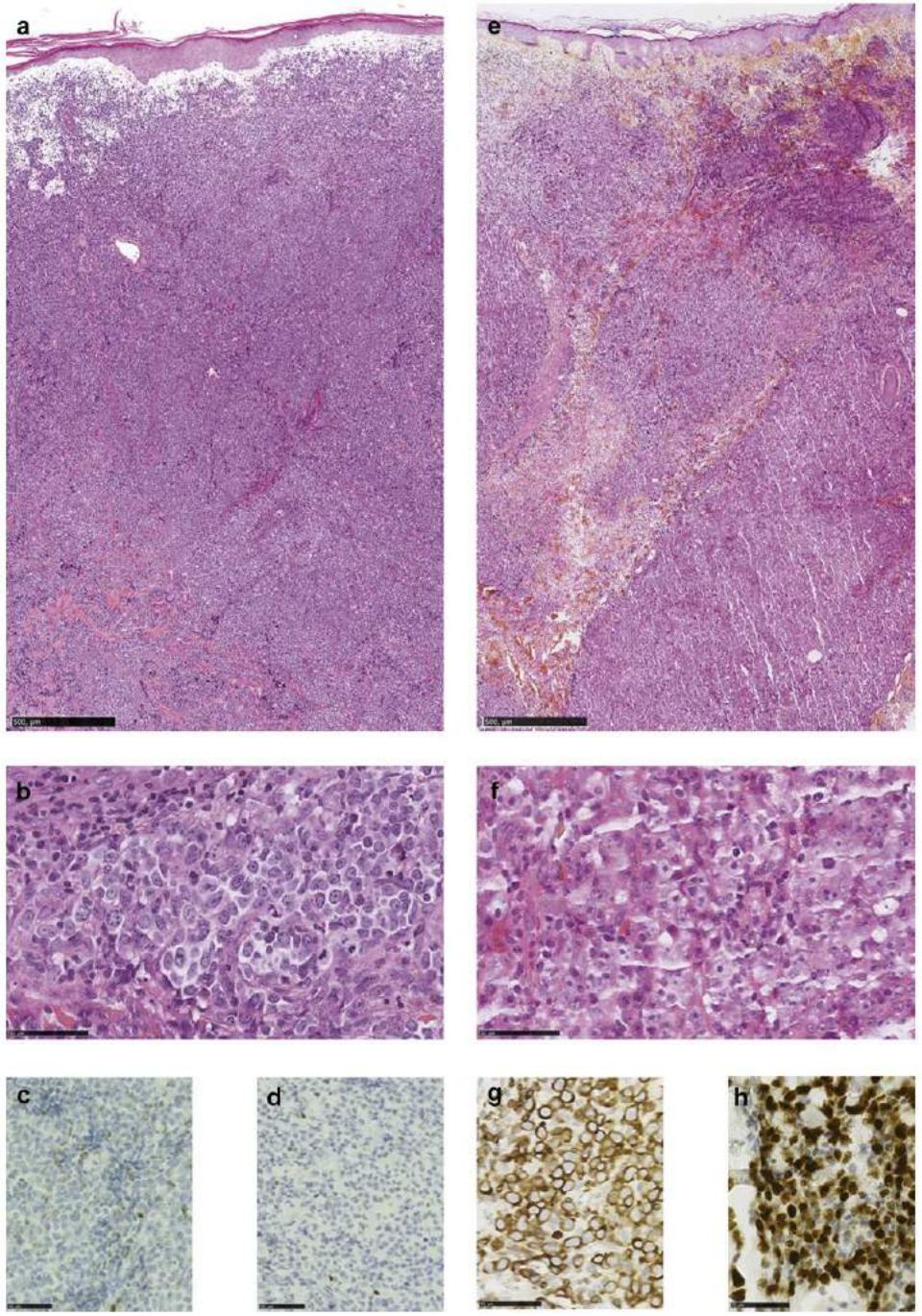


Figure 2. Algorithm for the diagnostic workup of aggressive B-cell lymphomas. The current algorithm for diagnosing aggressive large B-cell lymphomas starts with a biopsy collection from a lymph node (excision or needle biopsy) or a biopsy of an extranodal site. The diagnosis of the different lymphoma entities is based on a combination of morphology, immunophenotype, EBER in situ hybridization, FISH analysis, and B-cell clonality analysis. Advances in the understanding of DLBCL herald a transition to a molecular genetic classification (red arrow). This genetic classification is based on mutational profile, somatic copy number alterations, and structural variants. The depicted molecular subtypes were identified in 3 different studies indicating that these subgroups reflect true biological differences.[131,132,134] On the basis of these molecular studies, a predictor model was developed that dissects the cell-of-origin and stratifies further the molecular classification into 7 genetic subtypes with apparently clinical relevance.[133] The acronyms indicate the names given in the different studies to the same identified biological group.

Primary cutaneous diffuse large B cell lymphoma, leg type

- The main problem is to distinguish primary cutaneous follicular lymphoma, diffuse pattern, from diffuse large cell B cell lymphoma, leg type
- Findings that help: age, sex, location
- Bcl2 (50% cut-off, as per Menguy et al)
- MUM-1 (80% cut-off, as per Menguy et al)



MYD88 Somatic Mutation Is a Diagnostic Criterion in Primary Cutaneous Large B-Cell Lymphoma

Journal of Investigative Dermatology (2016) **136**, 1741–1744; doi:10.1016/j.jid.2016.04.018

Menguy S et al

Primary cutaneous diffuse large B cell lymphoma, leg type

- In cases where MUM1 and bcl-2 do not help, mutations in *MYD88* may be of utility
  - Specificity and positive predictive value of 100%
  - Negative predictive value of 78% (Menguy et al)

Primary cutaneous diffuse large B cell lymphoma, leg type

- 5-year disease-specific survival of ~50%
- Worse survival: multiple sites on one or both legs
- Deletion of 9p21 (p16) by FISH or RT-PCR confers bad prognosis
- It appears that *MYD88* L265P is an independent marker for poor prognosis, similar to nodal DLBCL (Pham-Lenard, 2014)

Primary cutaneous diffuse large B cell lymphoma, leg type

- Patients are treated with chemotherapy (R-CHOP, with or without radiation therapy)
- Targeted therapies: lenalidomide, ibrutinib, nivolumab, bortezomib

Discussion

- Only a few (6) cases of spontaneous regression of DLBL-LT have been reported
- The mechanisms behind spontaneous regression are unknown
- Interactions between host immune system (T-cell response), tumor microenvironment, and apoptosis likely play a role
- Trauma induced by the biopsy may activate anti-tumor activity ??

Discussion

- Spontaneous regression is exceptional in aggressive non-Hodgkin lymphomas
- In DLBL it may occur in early stages of the disease
- Biopsy induced-trauma or infections (EBV, measles virus) have been associated with spontaneous regression
- Microenvironment (CD8+ TILs) may play a role in spontaneous regression, along with other factors such as inhibitors of metalloproteinases and angiogenesis

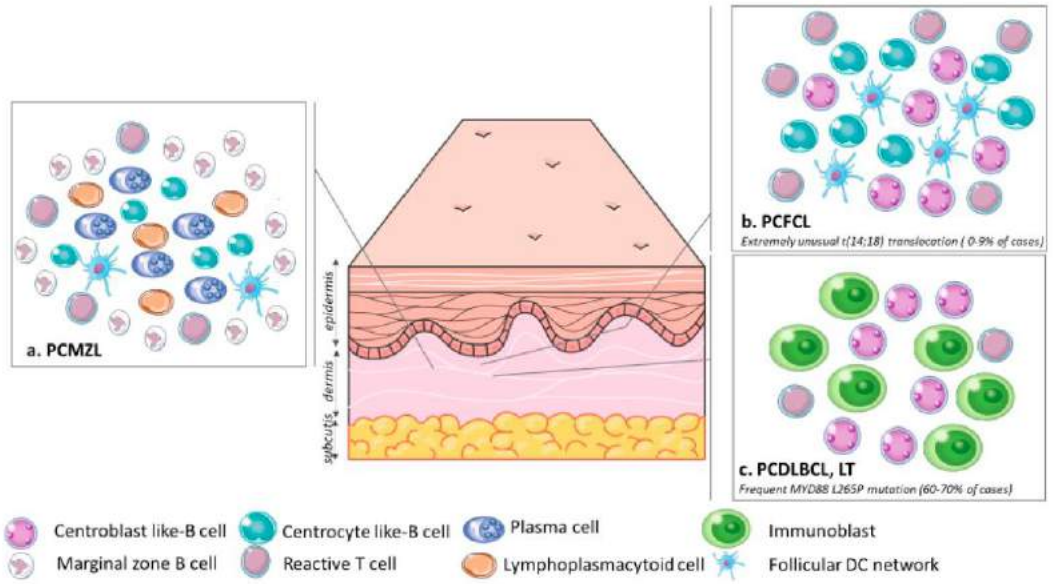


Figure 2. Organization of the tumor cells and microenvironment in (**a**). PCMZL: Infiltrate made of small centrocyte-like B-cells, lymphoplasmacytoid cells, plasma cells and reactive T cells admixed with a FDC network surrounded by marginal zone B cells; (**b**). PCFCL: Infiltrate made of centrocytes and centroblasts often with a FDC network and scattered reactive T cells; (**c**). PCDLBCL, LT: A monomorphic population of large atypical cells ressembling centroblasts and immunoblasts. The t (14; 18) translocation is extremely rare in PCFCL, unlike in primary nodal follicular lymphoma. The PCDLBCL, LT is characterized by frequent MYD88 L265P mutations, which helps discriminate PCDLBCL, LT from PCFCL with large cells, in which the MYD88 L265P mutation is absent. Abbreviations: PCMZL, primary cutaneous marginal zone lymphoma; PCFCL, primary cutaneous follicle center lymphoma; PCDLBCL, LT, primary cutaneous diffuse large B-cell lymphoma, leg type; DC, dendritic cell.

Dumont et al.

Cancers **2020**, *12*, 1497

Primary cutaneous diffuse large B cell lymphoma, leg type

- Microenvironment: Myeloid-derived suppressor cells (MDSCs) with PD-L1 coexpression and also immunosuppressive CD163+ M2 macrophages
- Expression of PD-L1 is frequent, and a subset of tumors have recurrent genetic alterations in PD-L1/PD-L2
- Tregs appear to be decreased in relation to indolent PCBCL

- 82 year-old woman with a history of one year of asymptomatic lesions on her right leg
- No systemic symptoms or lymphadenopathy
- Lab negative except for IgG positive for EBV and CMV
- Bone marrow biopsy was negative
- CT showed goiter and peritoneal lymphadenopathy or implant

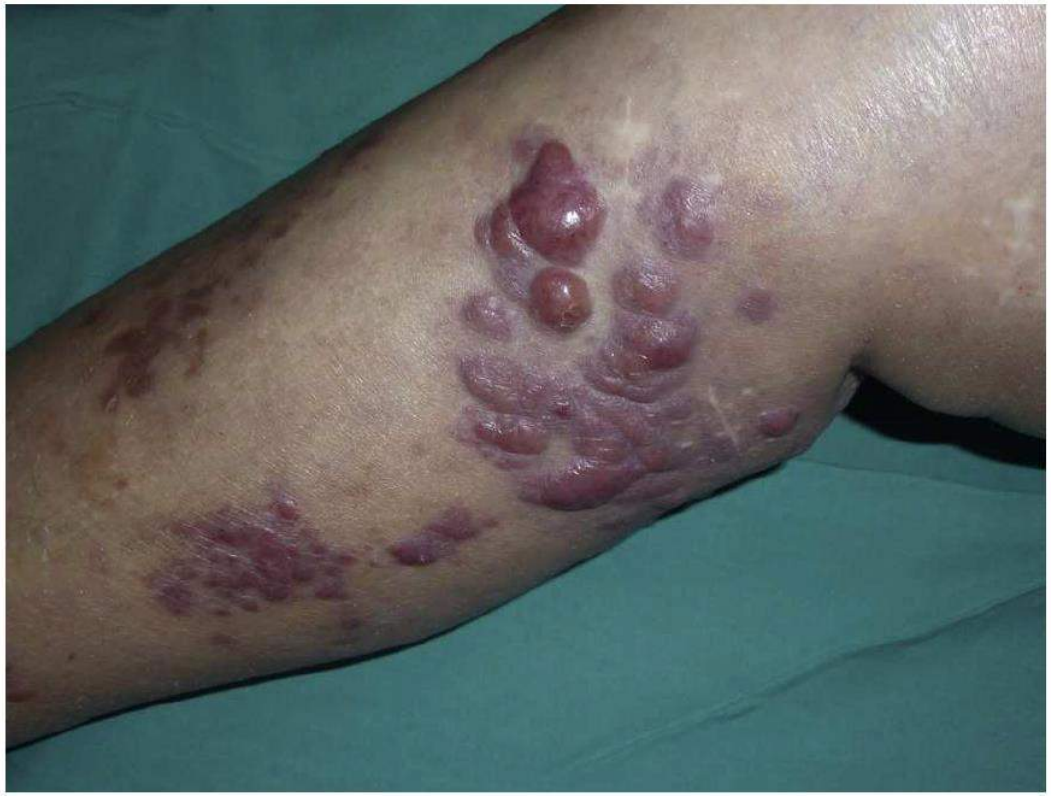
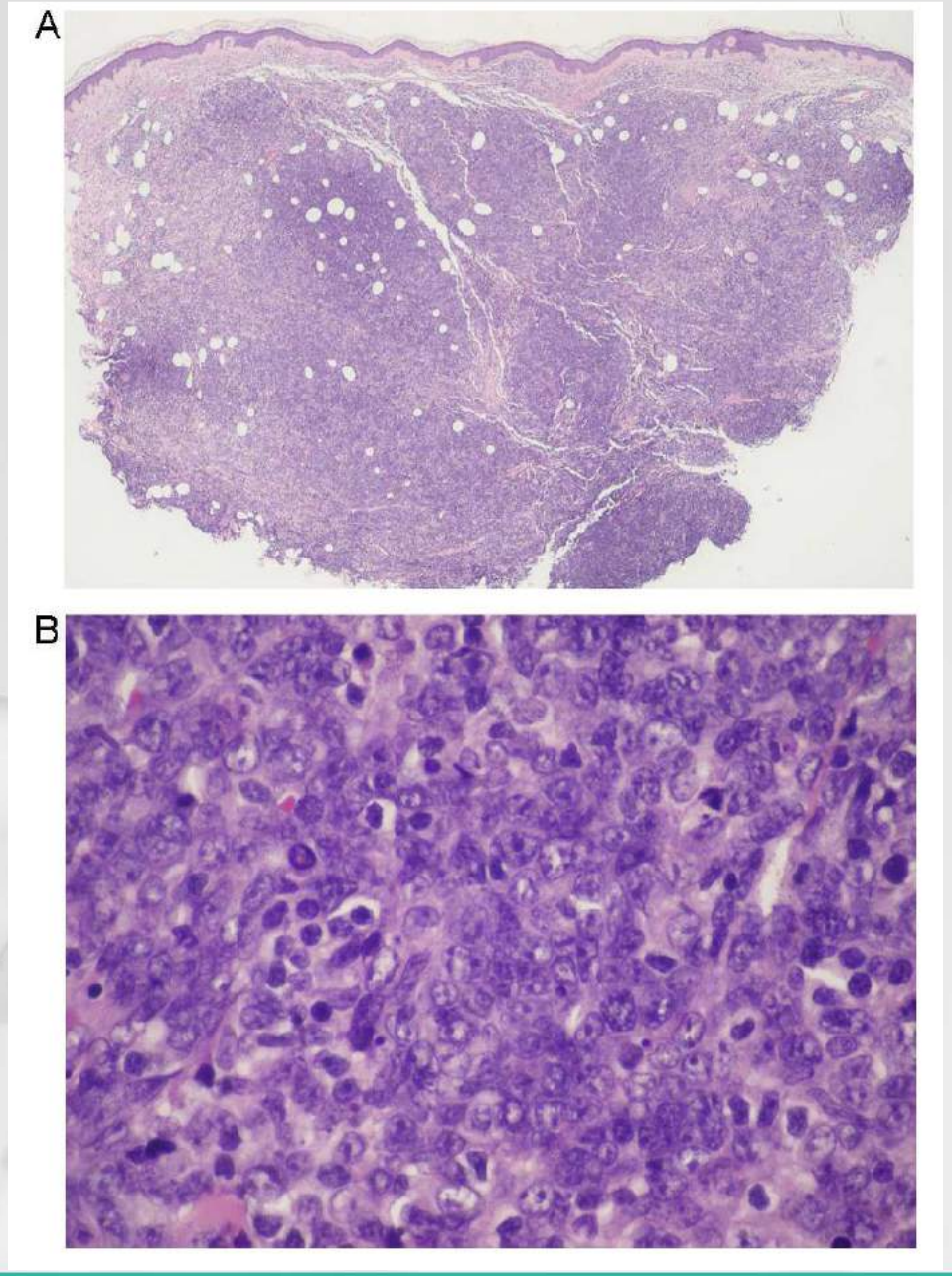


Figura 1 Tumores y nódulos eritematovioláceos, de consistencia elástica y de hasta 2 cm de diámetro localizados en la pierna derecha de la paciente.

J. Alcántara-González et al Actas Dermo-Sifiliográficas 2012



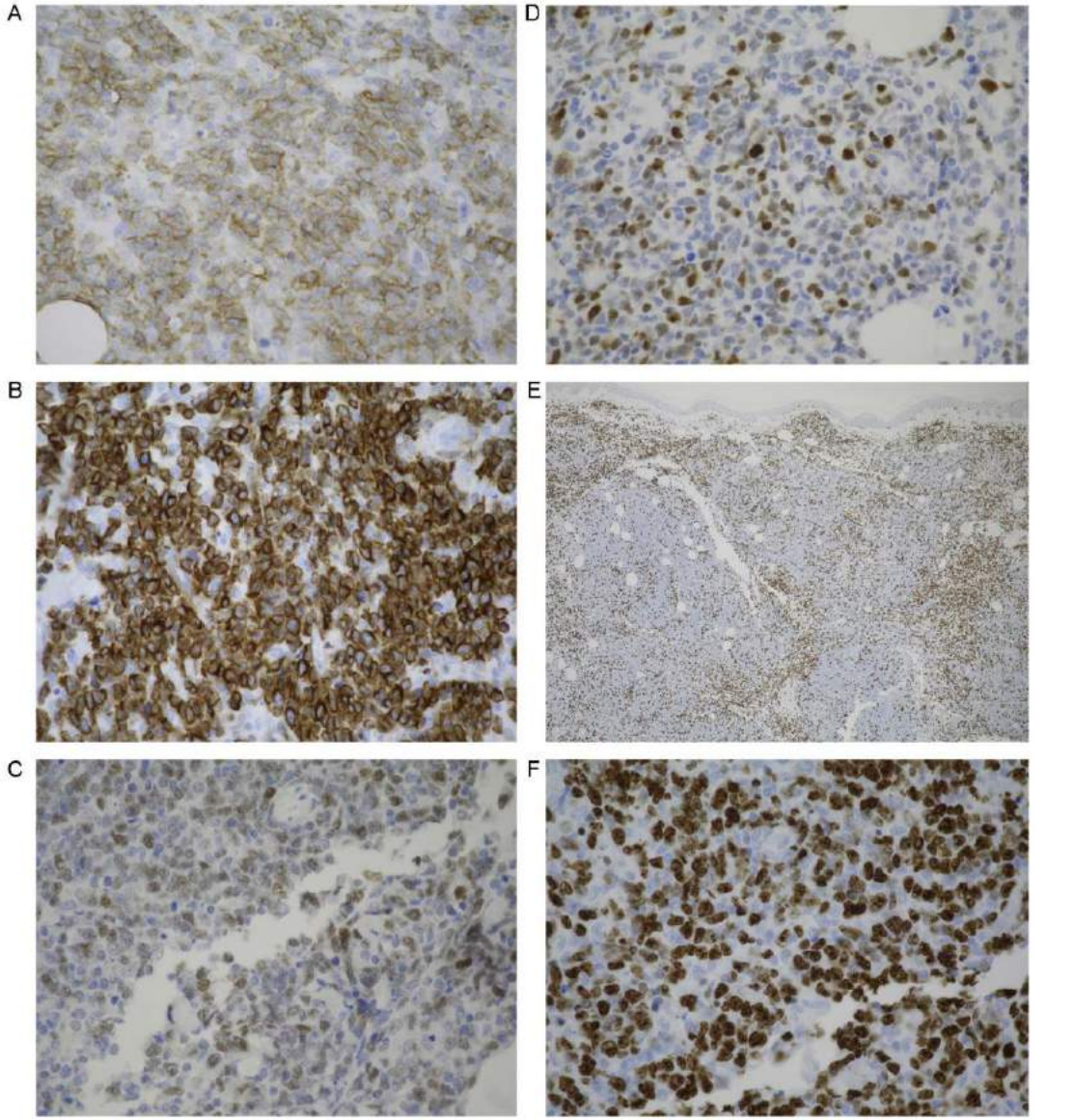


Figura 3 A. Positividad CD20 de las células neoplásicas, componentes predominantes del infiltrado (IHQ ×40). B. Positividad intensa para bcl-2 por parte de las células neoplásicas (IHQ ×40). C. Expresión de bcl-6 en las células neoplásicas que componen en el infiltrado (IHQ ×40). D. Expresión de MUM-1 (IHQ ×40). E. Positividad para CD3 por parte de las células de pequeño tamaño acompañantes (IHQ ×4). F. Expresión de Ki-67 marcada con un índice de proliferación estimado del 90% (IHQ ×40).

J. Alcántara-González et al

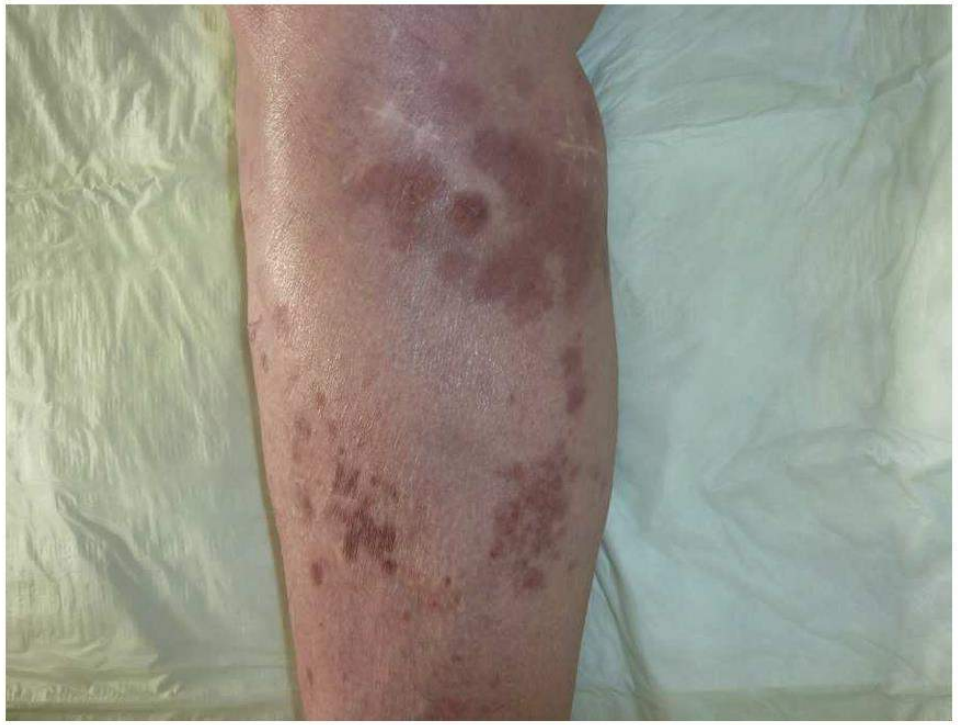


Figura 4 Máculas eritematoparduzcas de aspecto residual a las 4 semanas de la primera visita médica.

- Patient remained in remission for 4 months and then she passed away due to CVA

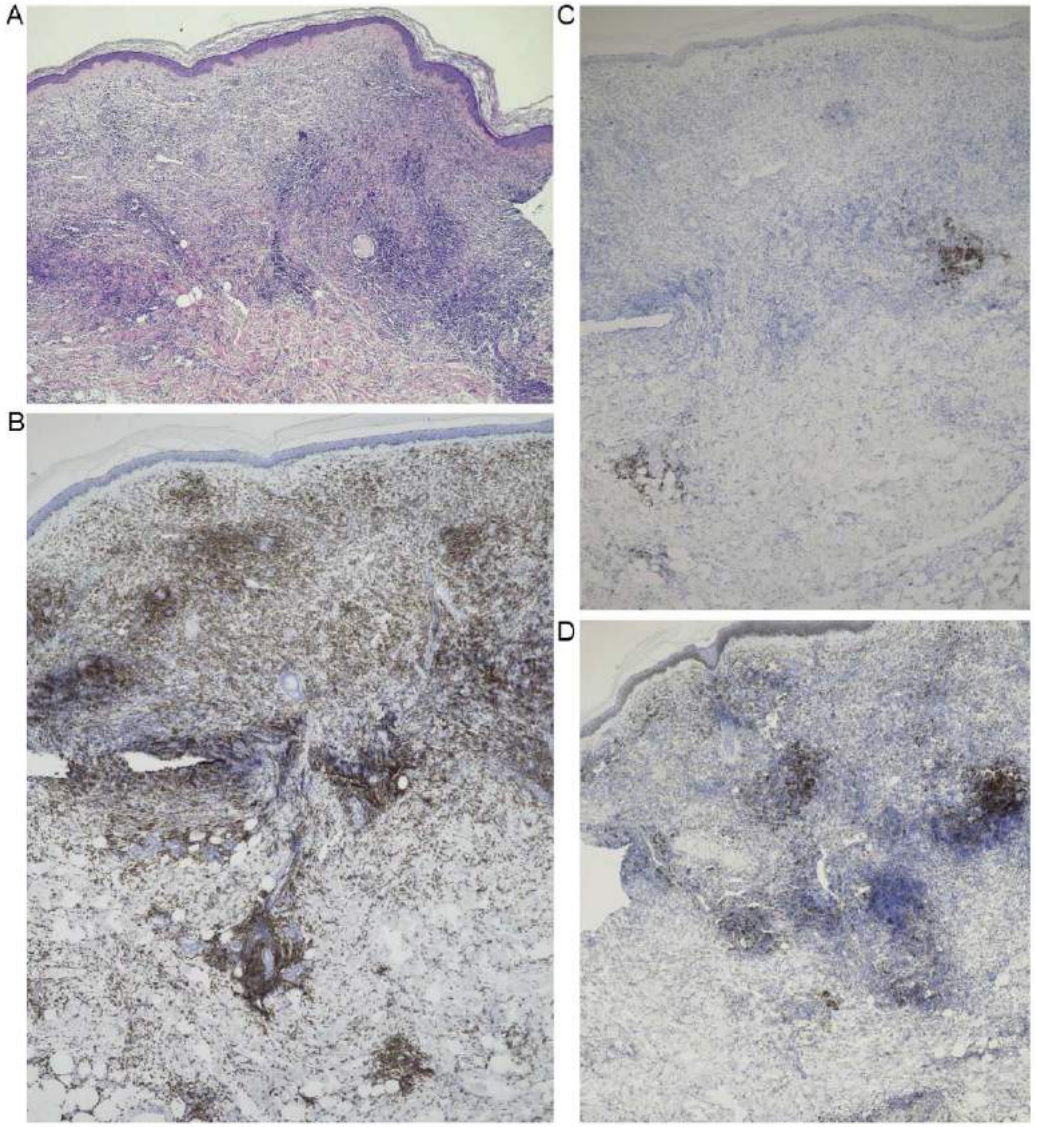
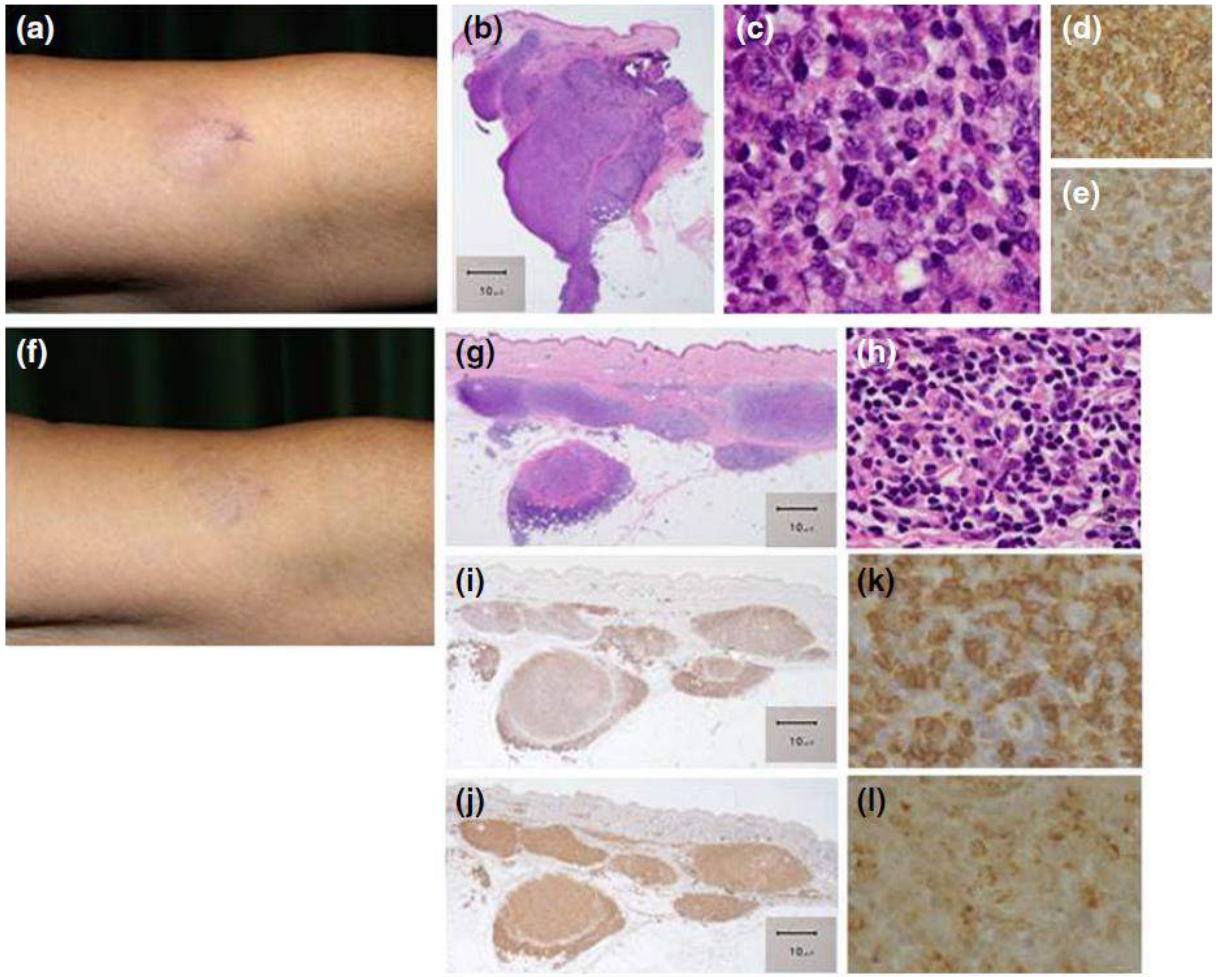


Figura 5 A. Infiltrado difuso compuesto por linfocitos T maduros con escasos focos de células atípicas (hematoxilina-eosina ×4). B. Expresión de CD3 por la mayor parte del infiltrado (IHQ × 4). C. Persistencia de focos de células CD20+ correspondientes a células atípicas (IHQ ×4). D. Persistencia de focos de células bcl-2+ correspondientes a células atípicas (IHQ ×4).

J. Alcántara-González et al

- A 72-year-old woman presented with a 3 cm single nodule on her left arm of one month duration
- The patient did not report any systemic symptoms
- No lymphadenopathy
- No history of autoimmune disease or immunosuppression
- The lesion regressed after biopsy and a new biopsy showed increased T cells (j), cytotoxic (perforin, l)



Jimura et al. J of Dermatology, 2016

- An 83-year-old woman presented with two lesions on her right leg of 8 month-evolution
- No lymphadenopathy
- LDH, β2 macroglobulin, CT scan, and bone marrow were negative (except for multinodular goiter)
- 3 months later the lesions showed regression and a new biopsy was taken

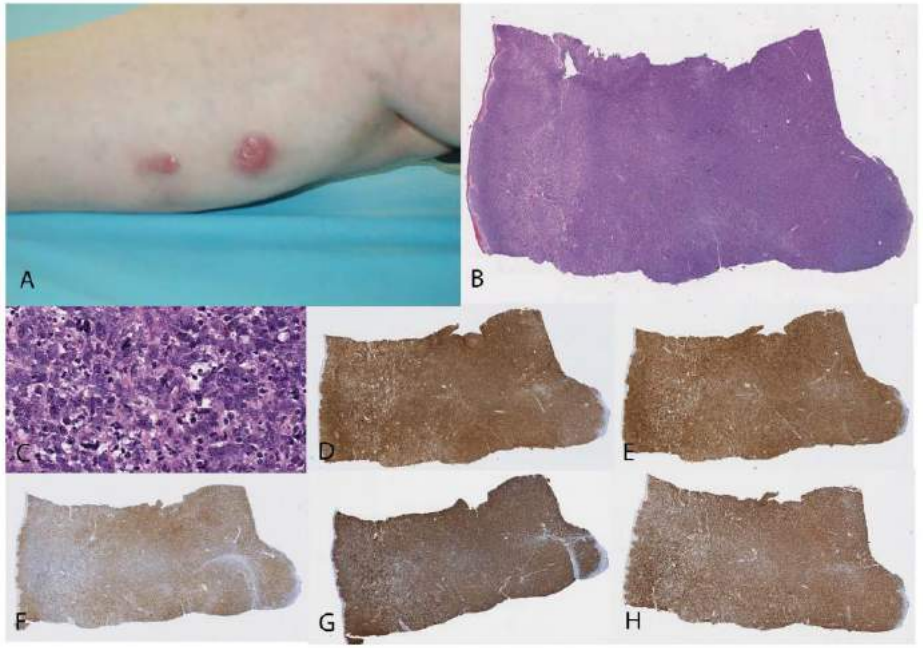


FIGURE 1. A, Orange indurated nodules on the back of right leg. B and C, Dense dermo-hypodermic cellular infiltrate sparing the papillary dermis, with immunoblast and centroblast type large cells and frequent mitotic figures [hematoxylin–eosin (HE), original magnifications: (B) ×1; (C) ×40]. The atypical cells were positive for (D) CD20 (×1), (E) Bcl2 (×1), (F) MUM-1 (×1), (G) Fox-P1 (×1), and (H) IgM (×1).

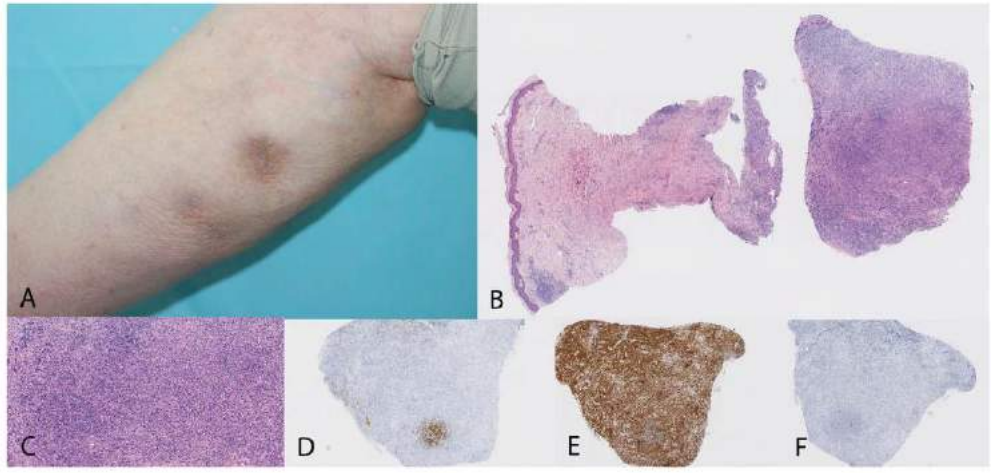


FIGURE 2. A, Brown residual macules in the area where nodules were previously located, 3 months after cutaneous biopsy. B and C, A mild dermo-hypodermic diffused lymphohystiocitary infiltrate with small-sized T lymphocytes is shown [HE: (B) ×2, (C) ×10]. D, Isolated focal points of $CD20^+$ cells (×4), (E) whereas a predominance of $CD8^+$ lymphocyte infiltrate is shown (×4). F, Mitosis seen with Ki-67 located in the $CD20^+$ areas (×4).

- 79 year-old man presented with a plaque on his left leg for one week
- Systemic workup was negative
- A biopsy was diagnosed as DLBCL-LT
- A month later the lesion improved without systemic therapy

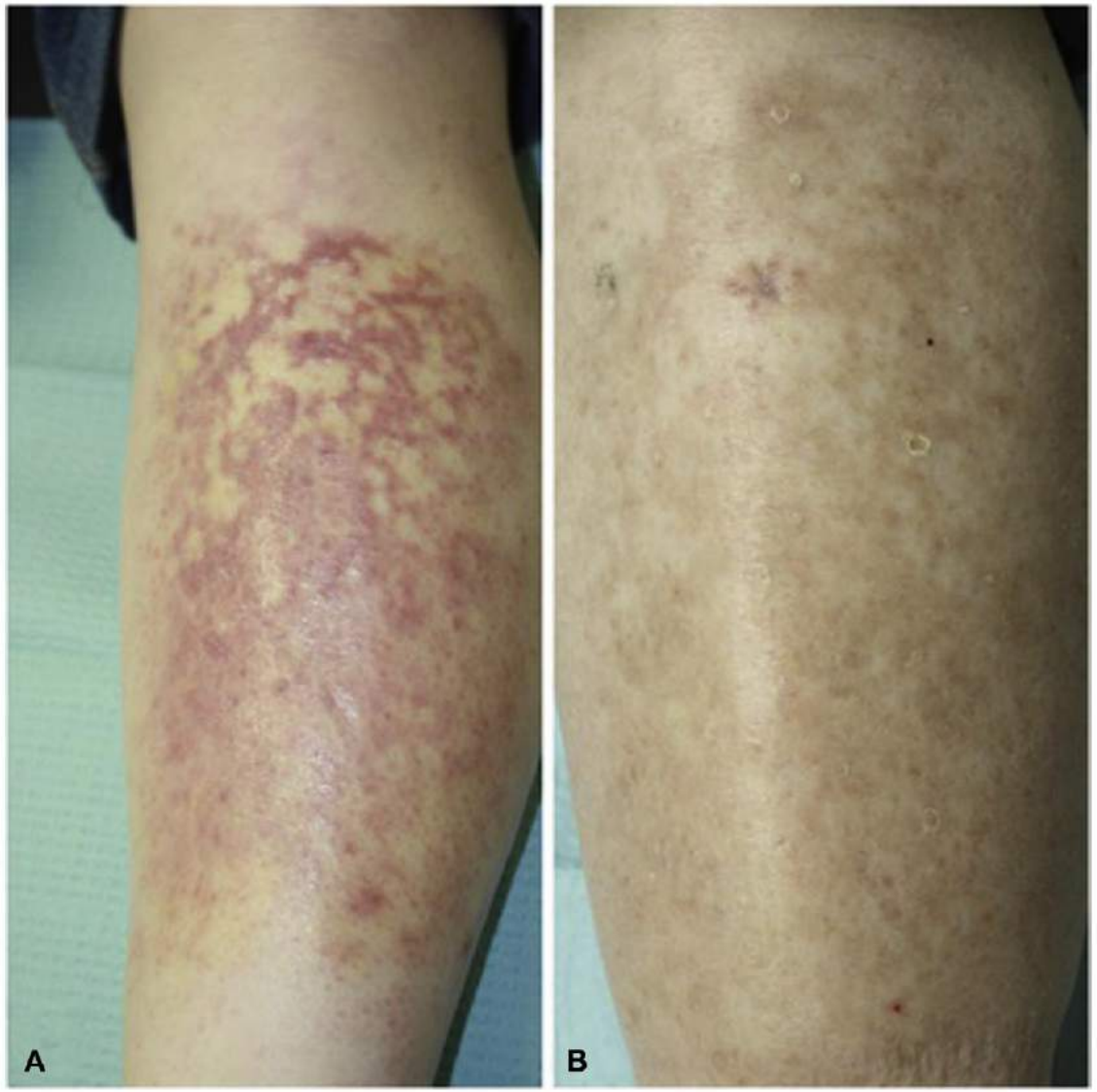


Fig 1. **A**, Five days after initial presentation: reticulated erythematous to violaceous plaque of the left anterior lower leg. **B**, Forty-five days later.

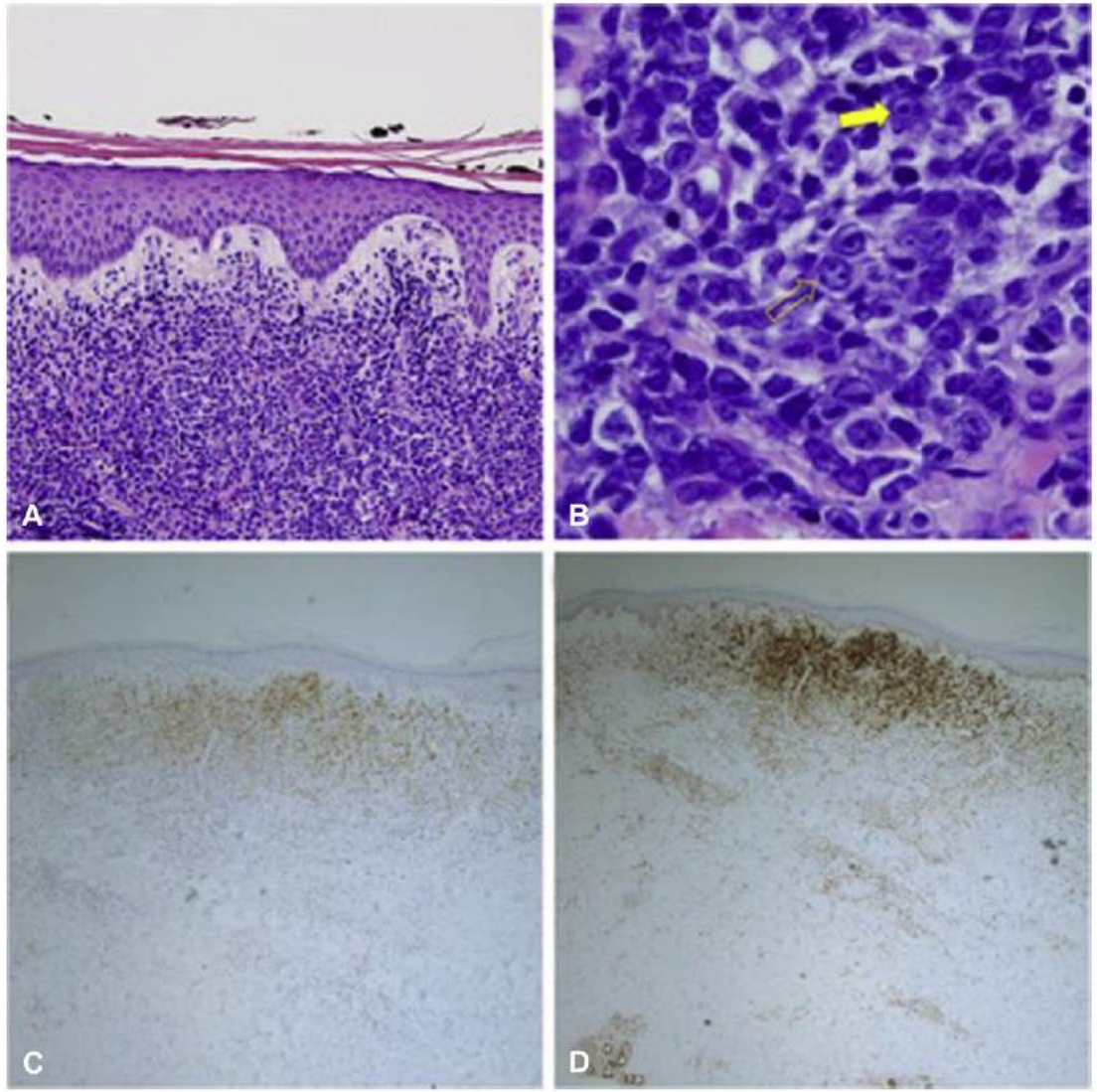


Fig 2. **A**, Diffuse lymphocytic infiltrate of the superficial and deep dermis separated from the epidermis by a Grenz zone. **B**, Immunoblasts (solid arrow) and centroblasts (open arrow). **C**, MUM1^{+} staining. **D**, Bcl-2^{+} staining. (Original magnifications: **A**, ×20; **B**, ×100; **C** and **D**, ×4.)

- A biopsy from the regressed area showed superficial and deep perivascular infiltrate composed of mature CD3-positive T lymphocytes
- CT scans and bone marrow biopsies were negative
- Patient declined therapy with R-CHOP
- He remained disease free of ~one year and then presented with a new plaque, confirmed as DLBCL-LT

- A 66 year-old man presented with a 6-week history of a purple tumor on his left lower leg
- No systemic symptoms, systemic workup negative
- Co-morbidities: diabetes mellitus type II, hypertension, chronic venous insufficience
- A biopsy was diagnosed as DLBCL-LT
- *MYD88* L265P was found
- Two months after biopsy the lesion spontaneously regressed, almost completely

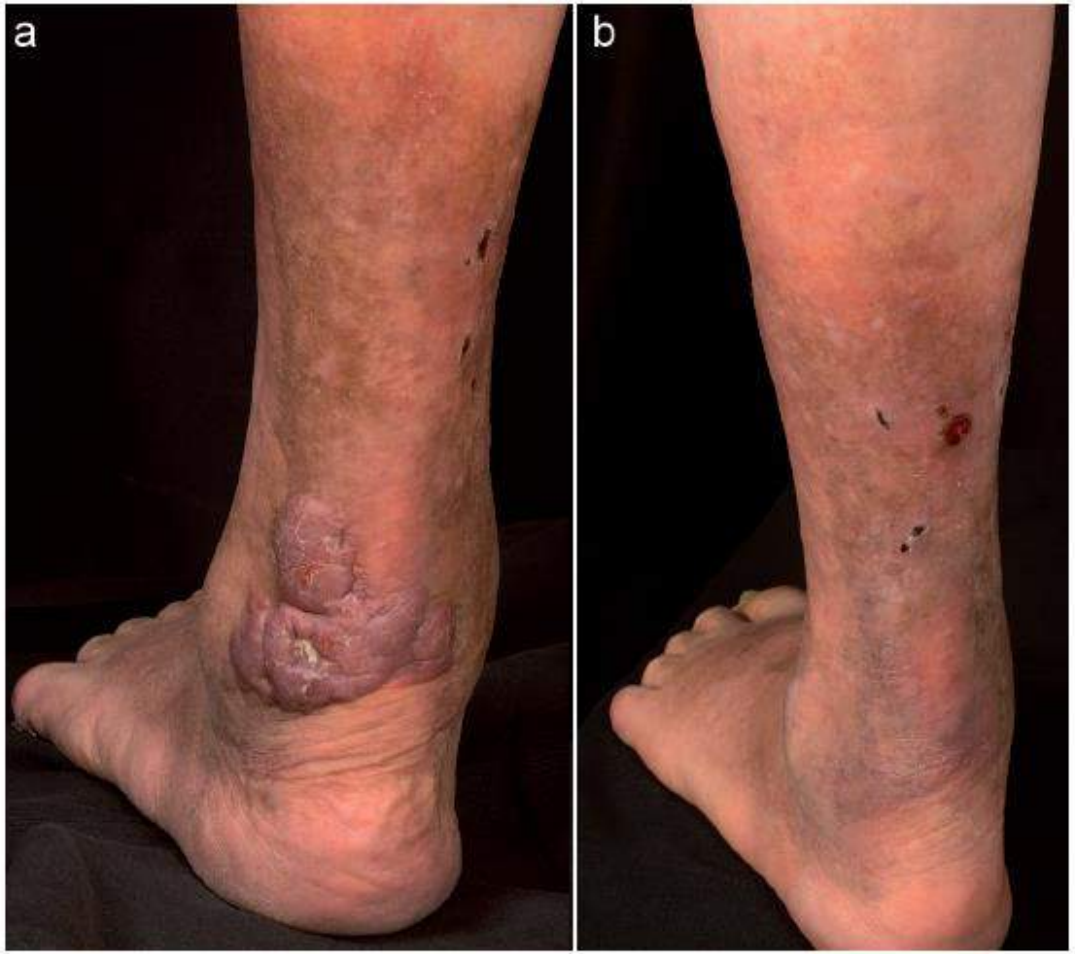


Fig. 1. Clinical course of spontaneous regression in a patient with diffuse large B-cell lymphoma, leg type. (a) Left lower leg before diagnostic biopsy showing a heavily infiltrated, purple coloured, nodular plaque covered by a few scales. (b) Spontaneous clinical regression 2 months after diagnostic biopsy.

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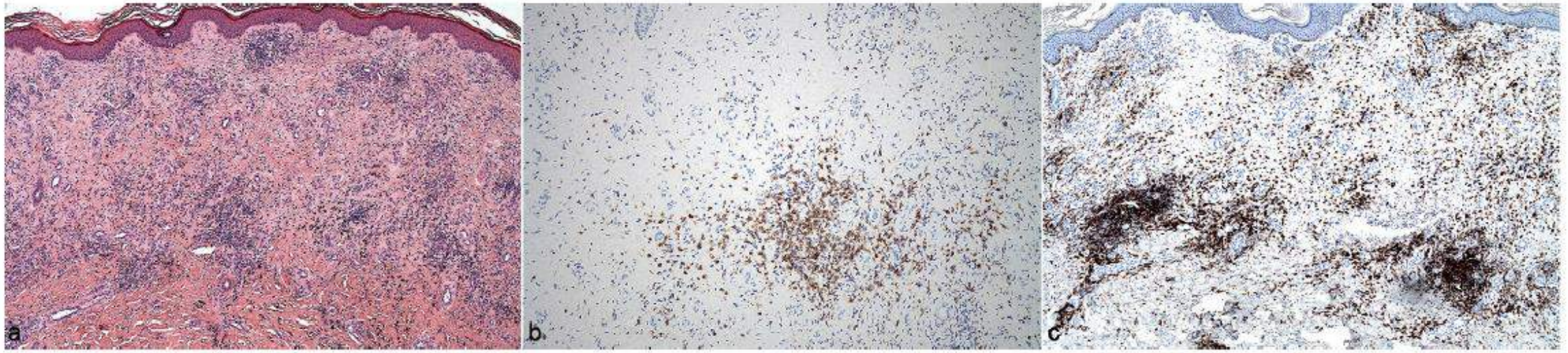

Fig. 2. Histopathological examination of a punch biopsy after spontaneous regression. (a) Section showing dermal fibrosis, telangiectatic vessels and numerous melanophages (haematoxylin & eosin, original magnification ×50). (b) CD79a staining shows remnants of neoplastic cells (original magnification ×100). (c) CD8 staining reveals numerous $CD8^+$ T-cells (original magnification ×50).

- A biopsy from the regressed area showed scattered residual lymphoma cells and numerous CD8-positive T lymphocytes
- Radiation therapy was initiated to achieve complete remission

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- A 62-year-old man complained of five painless nodules on his left leg for a month
- The lesions started as small red papules which rapidly grew
- No systemic symptoms
- Laboratory workup was negative
- Bone marrow, PET scan were negative
- Patient declined therapy since the lesions began to resolve after biopsy

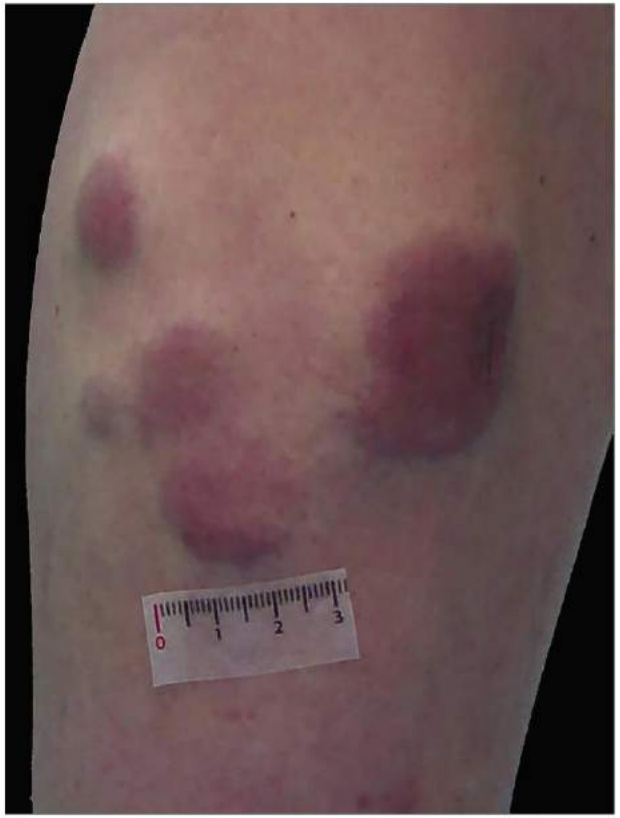


Figure 1a: Five erythematous, indurated and infiltrated nodules and tumours on the left leg

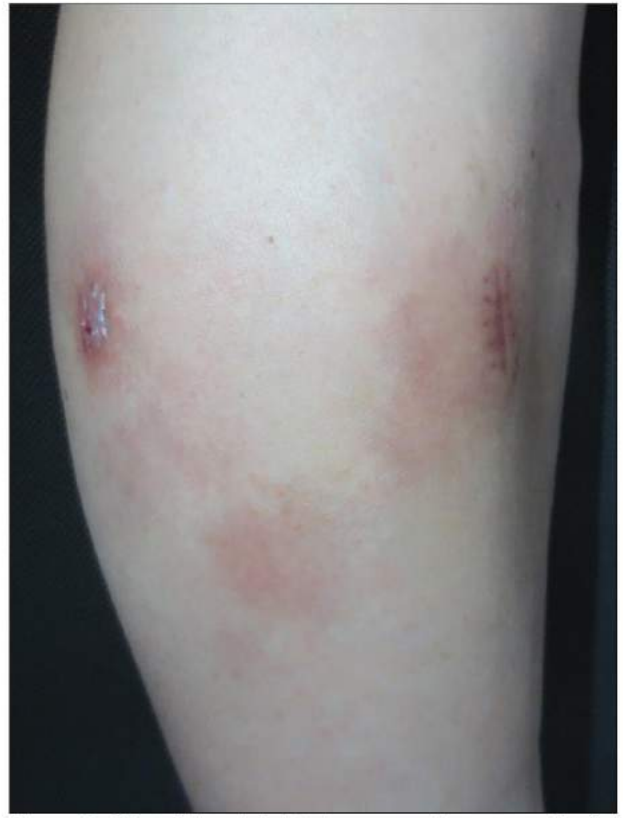


Figure 1b: Most of the original lesions regressed spontaneously after 3 months, leaving varying degrees of pigmentation

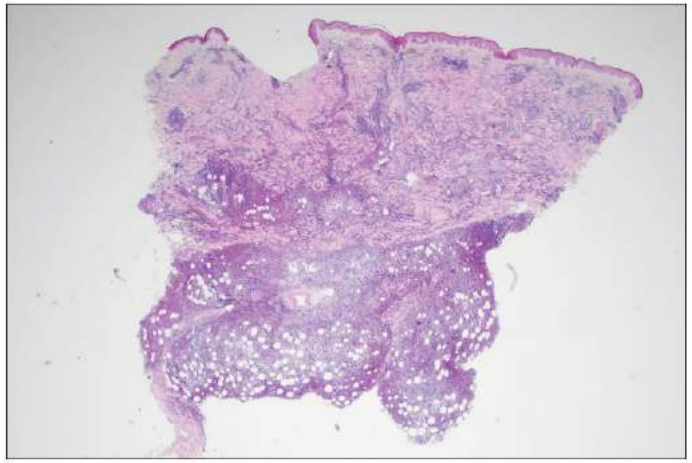


Figure 2a: A diffuse infiltration distributed throughout the dermis and subcutis (haeamatoxylin and eosin stain, ×12.5)

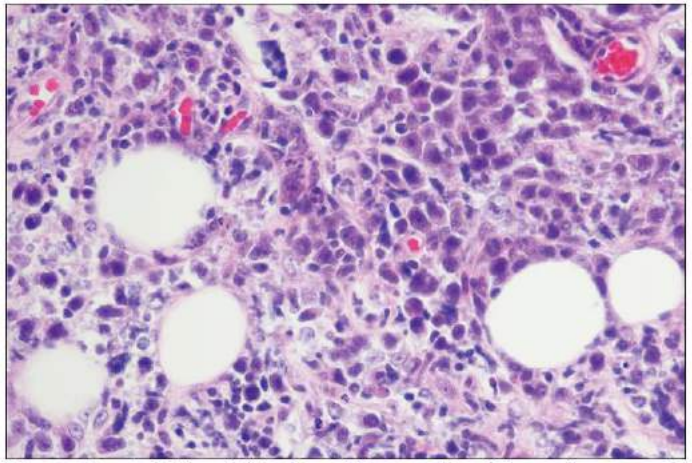


Figure 2b: A diffuse infiltration of large cells with prominent nuclei distributed throughout the dermis and subcutis mainly including centroblasts and immunoblasts (haematoxylin and eosin stain, ×400)

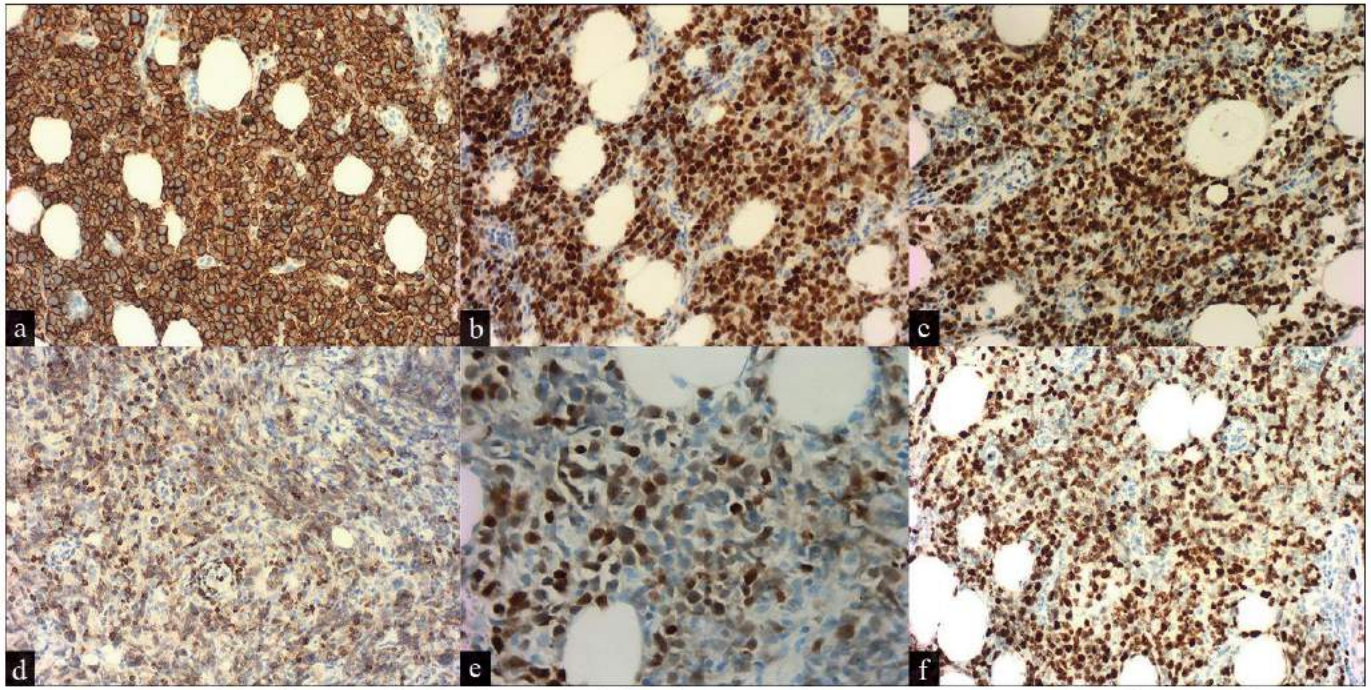


Figure 3a–f: The neoplastic cells were positive for (a) CD20 (x200), (b) Bcl-6 (×200) and (c) PAX-5 (×200). The neoplastic cells were partial positive for (d) Bcl-2 (×200) and (e) Mum-1 (×400). (f) The Ki-67 proliferation rate was around 60% (×200).

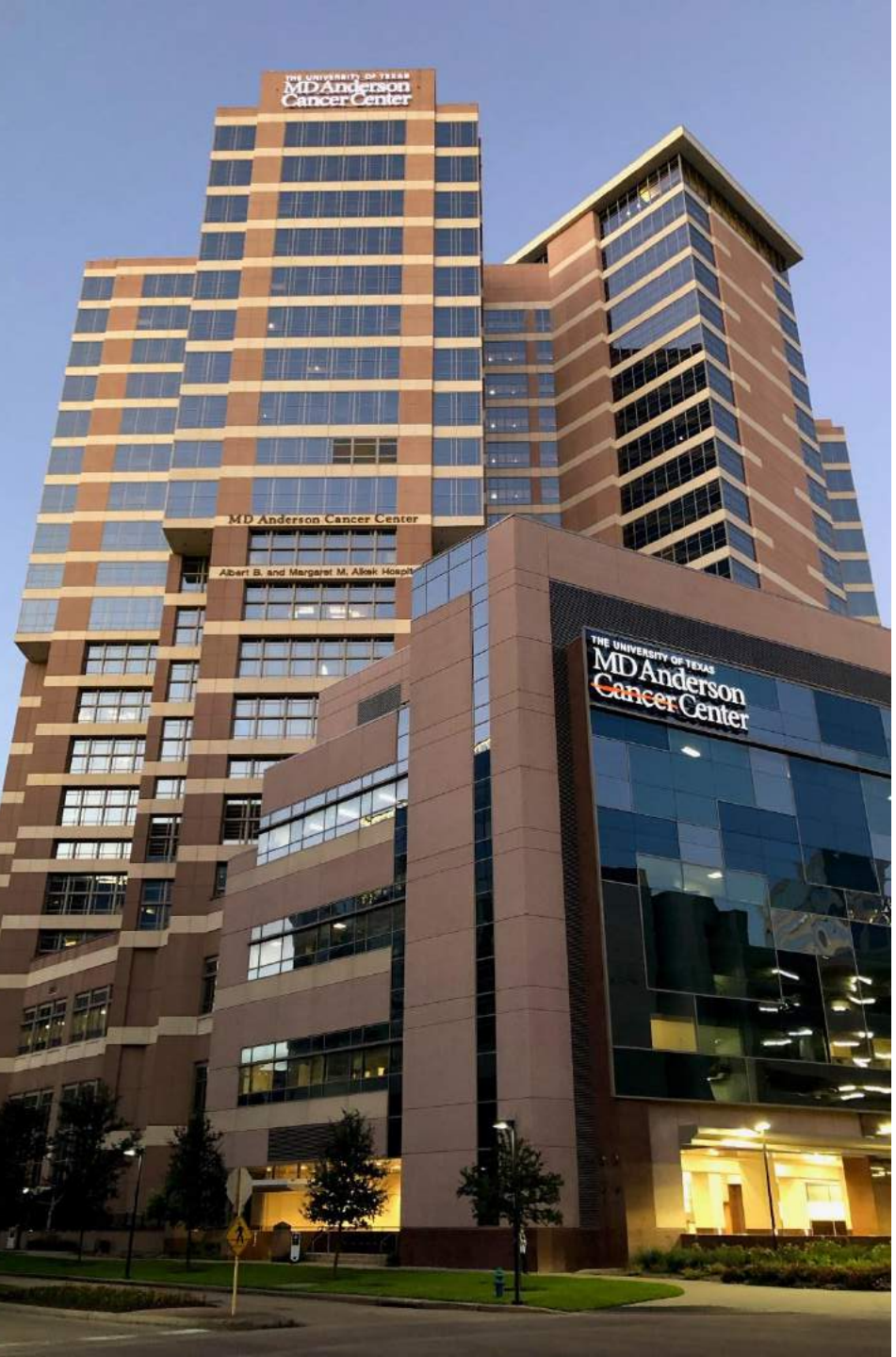
Table 1: Cases of primary cutaneous diffuse large B-cell lymphoma, leg type that showed spontaneous regression without anti-neoplastic treatment

Case	Age/sex	Location	Skin lesions	Symptoms	Evolution of the lesions	Inflammatory cells in repeat biopsy during tumour regression	Complementary therapy	Outcome	Relapse
1[2]	82/F	Right leg	Multiple nodules and tumours	No	Almost disappeared after 4 weeks	Diffuse mature T cells (CD3+)	None	CR for 4 months until died of a cerebrovascular accident	No
2[3]	72/F	Upper left arm	Solitary tumour	No	Apparently shrank after the biopsy	Many small lymphocytes (positive for CD3, CD4, CD8, perforin, granzyme B and TIA1)	Surgery	CR for 21 months after surgery	No
3[4]	83/F	Back of the right leg	2 erythematous nodules	Local pain	Regressed at 3 months after biopsy	Small-sized T lymphocytes (positivity for CD2, CD3, CD4, and predominantly CD8)	Radiotherapy	CR for 1 year after radiotherapy	No
4[5]	66/M	Lower left leg	Solitary tumour	No	Regressed after 2 months	Significant CD3+ T cells	Radiotherapy	ND	ND
5[6]	79/M	Anterior left leg	An erythematous reticulated plaque	No	Resolved 1 month later	Predominant CD8+ T-cells	None	CR for more than 1 year but ultimately relapsed	Yes
6*	62/M	Posteromedial left leg	5 erythematous nodules	No	Regressed after 3 months	ND	None	CR for 60 months	No

*The last one is our case. F: female, M: male, CR: complete remission, TIA1: cytotoxic granule associated RNA binding protein, ND: not described

Conclusions

- Primary cutaneous diffuse large B cell lymphoma, leg type is a distinct type of DLBCL, with unique clinical, pathological, and molecular features
- PCDLBCL-LT is an aggressive lymphoma, as opposite as other primary cutaneous B cell lymphomas/lymphoproliferative disorders
- Spontaneous regression is a rare phenomenon that suggests a role for tumor microenvironment and immune response in the control of this disease
- Therapies targeting immune response and TME appear to be reasonable in these cases



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