Large Cells With CD30 Expression and Hodgkin-like Features in Primary Cutaneous Marginal Zone B-Cell Lymphoma

A Study of 13 Cases

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黏膜相关结外边缘区B细胞淋巴瘤 MALT

- 定义：一种结外淋巴瘤，由形态不均一的小B细胞组成，包括边缘区（中心细胞样）细胞，单核样细胞，小淋巴细胞，散在的免疫母细胞及中心母细胞样细胞。某些情况下，可存在浆细胞分化。肿瘤细胞可位于反应性滤泡的边缘区，并可延伸至滤泡间区和滤泡。在上皮组织中，肿瘤细胞通常浸润上皮，形成淋巴上皮病变。
- ICD-O code 9699/3
- 发病率：占B细胞淋巴瘤的7-8%，好发于成年人（中位年龄70岁）。
- 部位：胃（35%）最常见，其次是眼睛和眼附属器（13%），皮肤（9%），肺（9%），唾液腺（8%），乳腺（3%）和甲状腺（2%）。

2016 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Introduction

- PCMZL: pimary cutaneous marginal zone lymphoma.
- Included in the group of extranodal marginal zone lymphoma.
- Indolent cutaneous B-cell lymphoma: most local recurrence, sporadic cases show extracutaneous dissemination or large tumoral masses.
- Few prognostic markers for differentiating patients.
- PCMZL : CD30+ large cells, sometimes with Hodgkin-like morphology.

Aim

- Investigate the presence of CD30+ large cells and Hodgkin-like cells, and their possible link with progression in PCMZL;

- Investigate their relationship with the presence of atypical T cells and of TCR and IgH gene rearrangements.

MATERIAL AND METHODS

Case Selection :

- ✓ Fundación Jiménez Diaz University Hospital of Madrid, Spain; 2000 ~ 2018; skin biopsies.
- ✓ All cases featuring ≥10% CD30+ large cells, most had large pleomorphic cells(R-S-like/Hodgkin-like).
- ✓ Diagnosis: 2017 WHO classification, none had systemic Hodgkin lymphoma.

Histopathologic Assessment:

- ✓ Histologic pattern:

  perivascular/periadnexal, nodular, diffuse, or mixed
- ✓ Proportion of large CD30+ tumoral cells (CD30+/CD20+); Pattern of CD30 staining: scattered, clustered, or diffuse.
- ✓ Reactive follicles, light-chain restrictions and dominant heavy chain.

MATERIAL AND METHODS

- **Immunohistochemistry:**

  CD30,CD15,CD20,CD3,PD1, κ, λ, IgG, IgM, IgD, IgA, CD123, Bcl6, Bcl2, p53, Pax5, CD21, CD23, CD5, Ki67, MYC, and pSTAT3

- **In Situ Hybridization:** EBER(Ventana)
- **Molecular studies:**

  PCR for IgH, TCR Gene Rearrangement

  Other Genotypic Studies: target genes related to low-grade B-cell lymphoma.

- **Statistical Evaluation**

RESULTS

Clinical Presentation

- ✓ 13 cases (10 male and 3 female); 30-79y (54y);
- ✓ Lesions: nodules, agminated papules, raised plaques or large tumoral masses (case 3);
  site: extremities (5/13), followed by trunk (4/13).
- ✓ Staging system of EORTC/ISCL: 4 patients had early located disease, others advanced disease.
- ✓ None: extracutaneous involvement in image tests or bone marrow biopsies; systemic Hodgkin lymphoma.
  (*Ex*. Patient 9: testicular DLBCL for 7 years)
- ✓ Follow-up time: 3 months to 24 years(54 months)

RESULTS

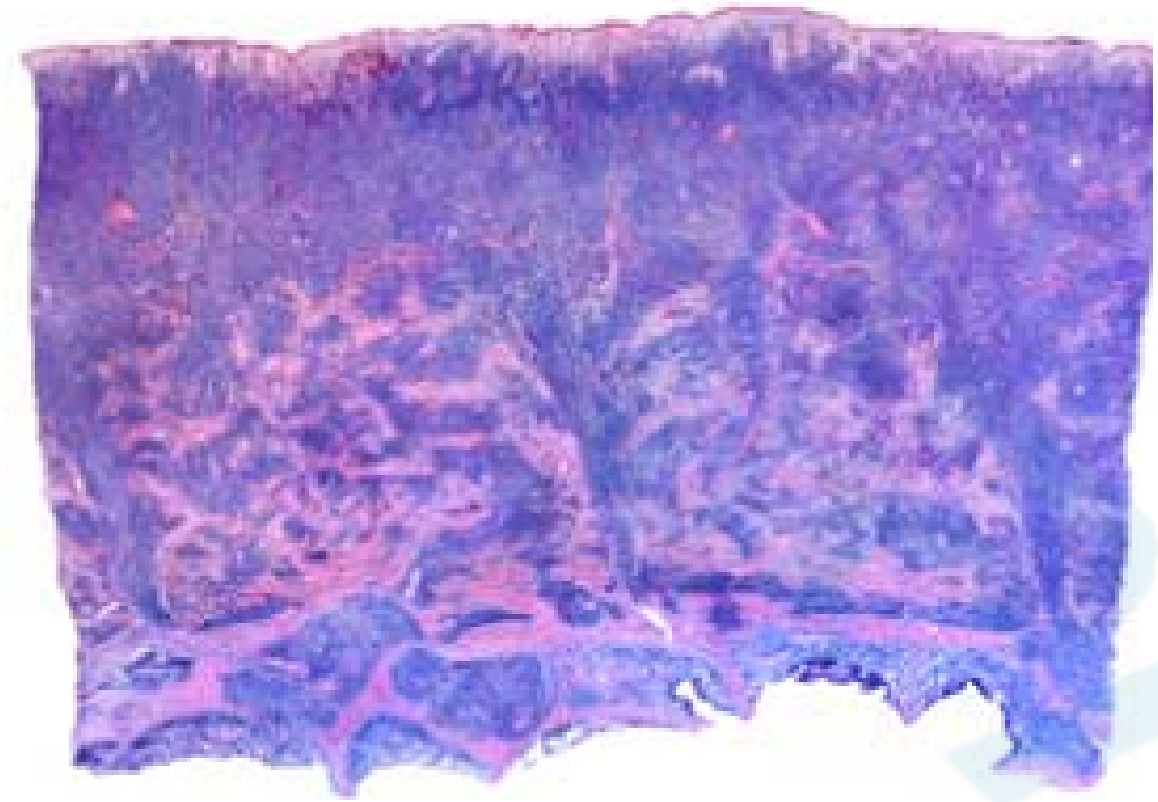
➢ Histopathologic and Immunophenotypic Features

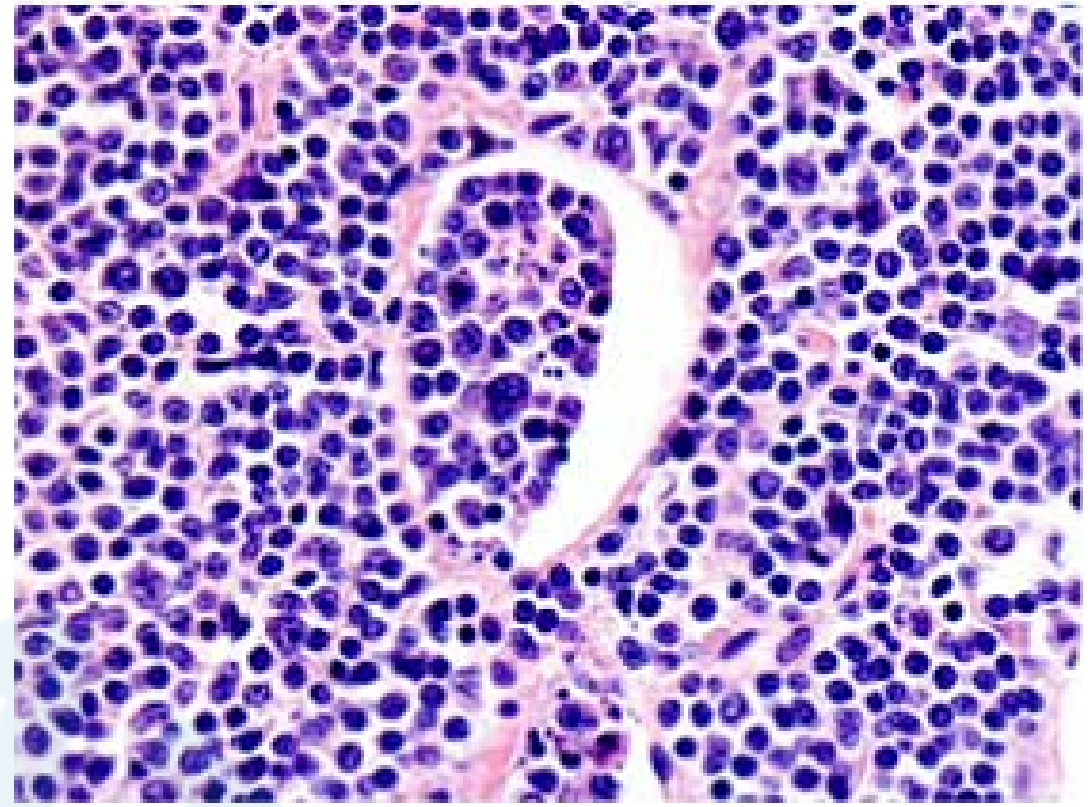
1. 11 cases: nodular pattern; 2 cases: diffuse distribution.
2. All cases: diffuse T infiltrate, 69% T-cell rosettes.

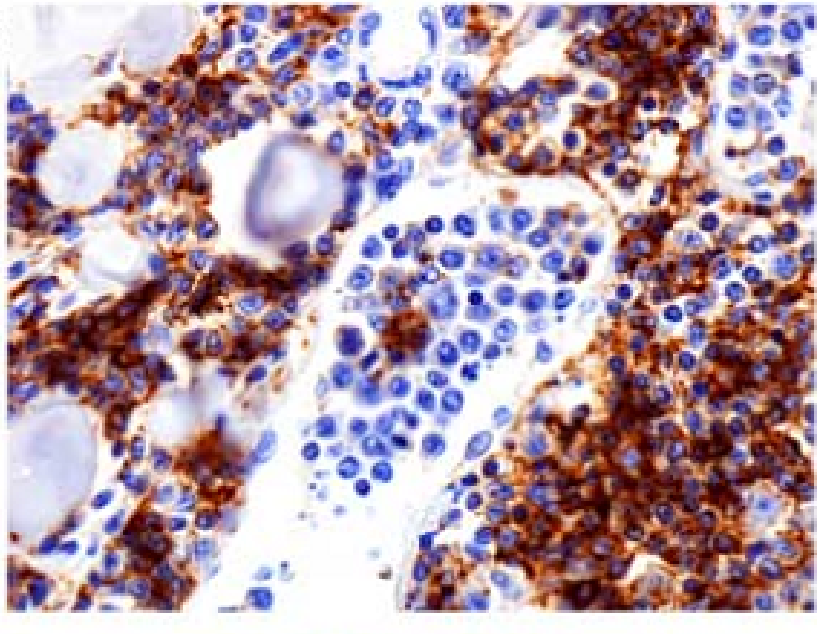
   PD1+ T cells (atypical morphology) around CD30+ Large cells.
3. Reactive follicles with partially colonized germinal centers.
4. Tumoral B cells: CD20, Pax5, and Bcl2+; Bcl-6 and CD10-
5. EBER-: ruling out CD30+ lymphomas related to EBV infection.
6. CD30+ cells: scattered, clustered, or occurred diffusely;

   Most had immunoblast cytology, rarely Hodgkin-like morphology

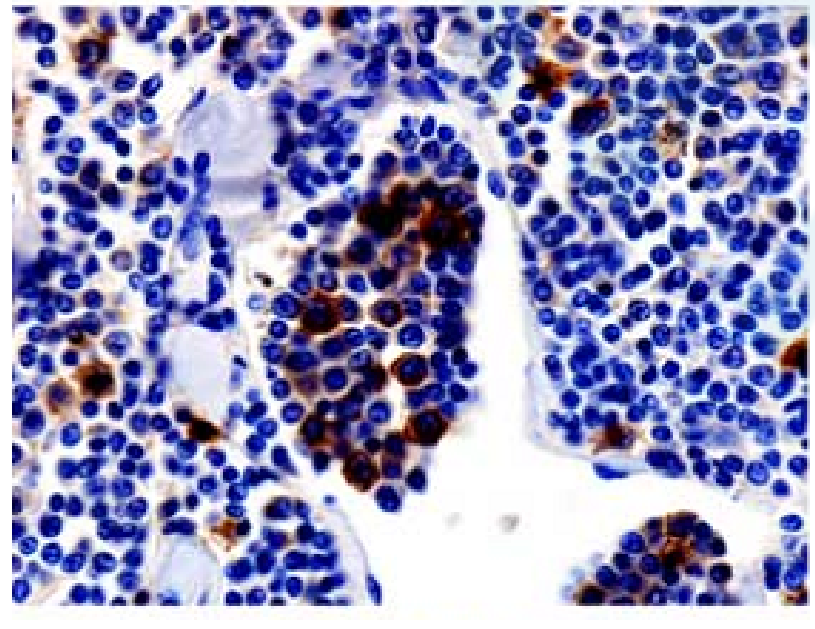
Patient 3: first biopsy



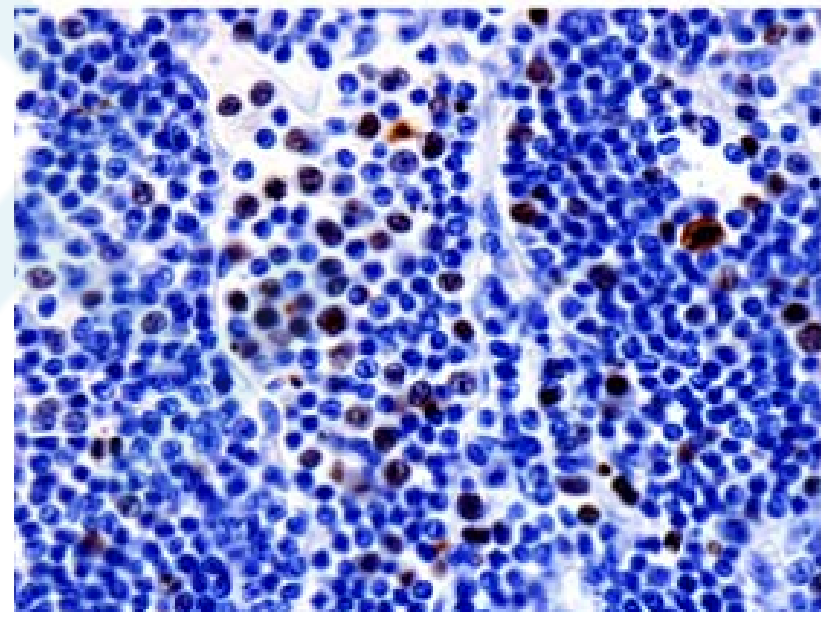




CD20

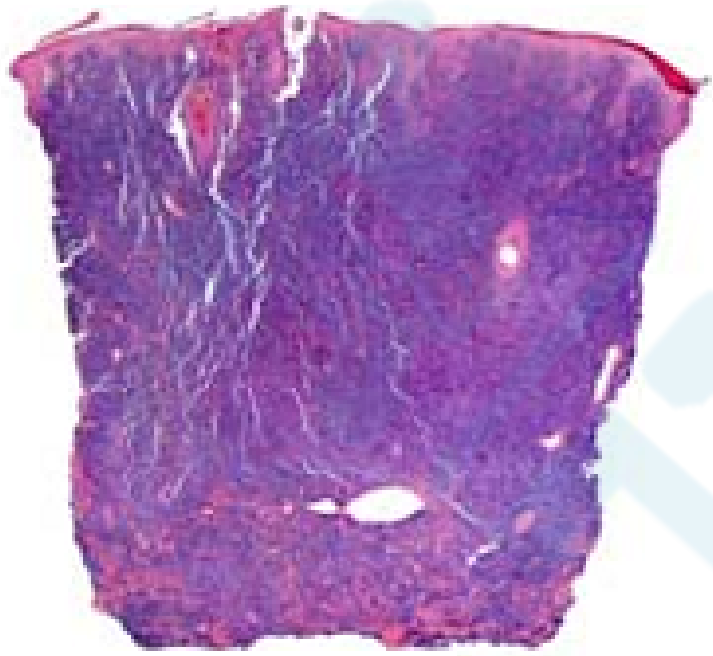


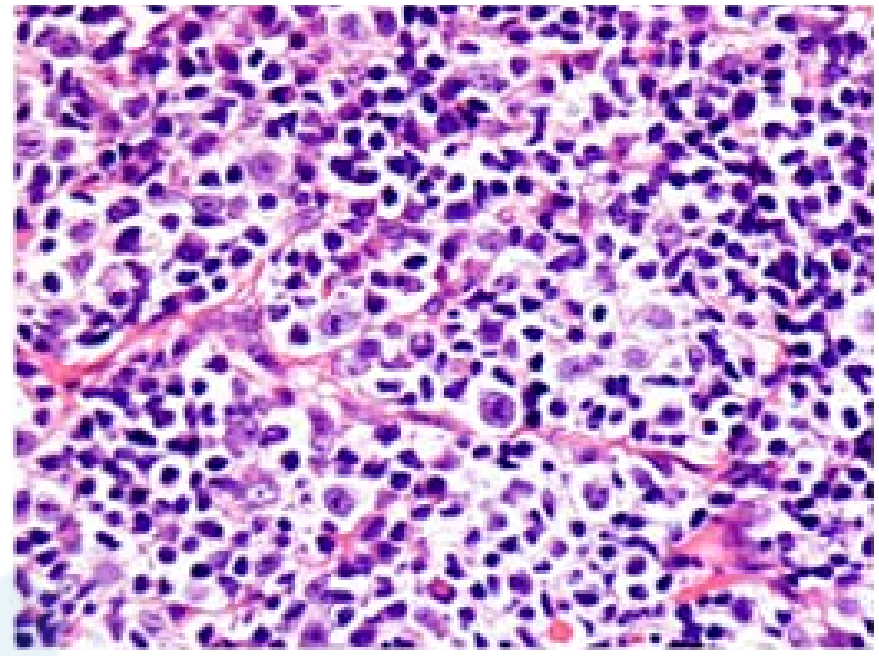
CD30



Ki67

Patient 3: second biopsy





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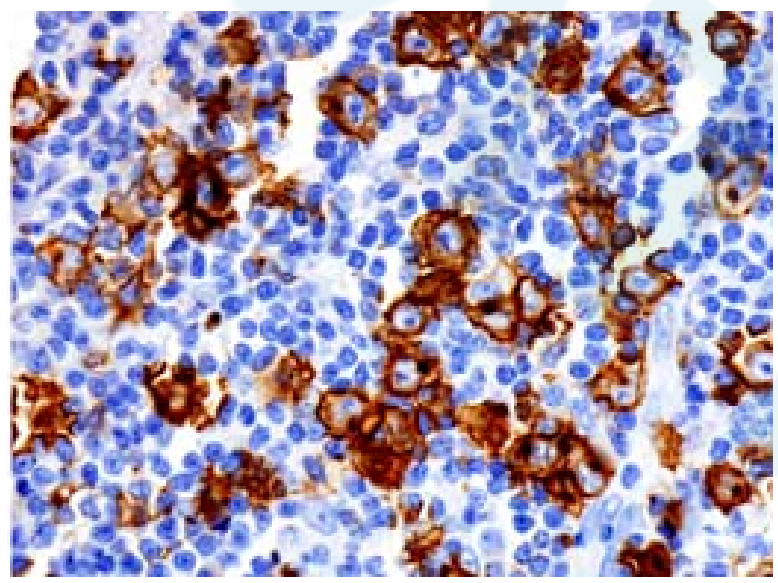
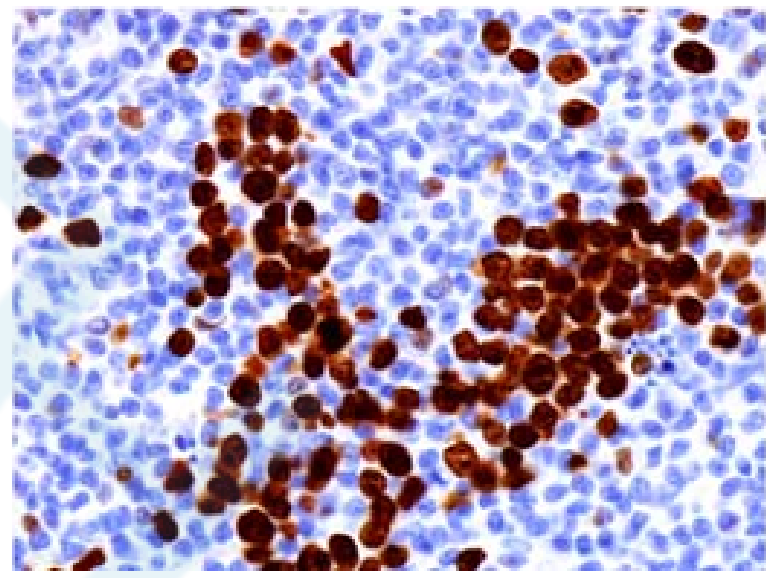
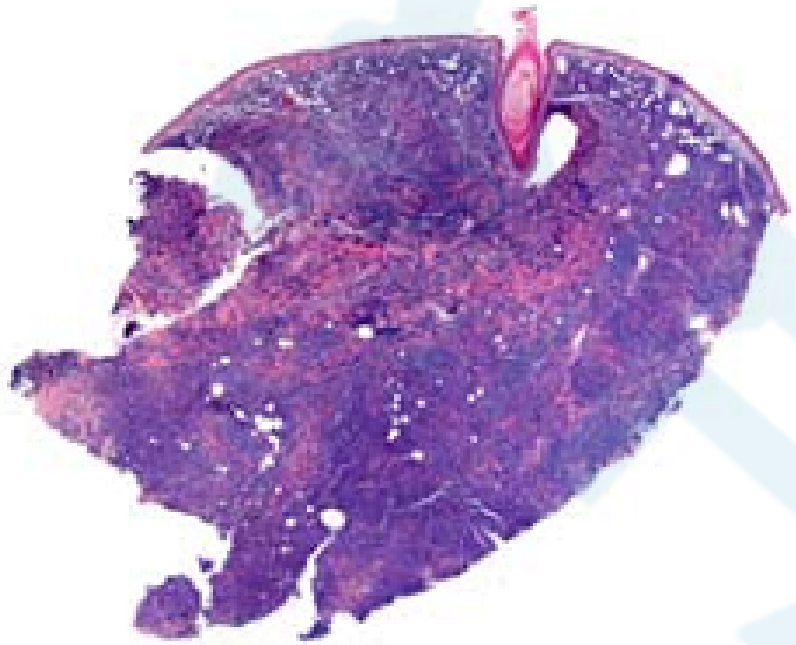


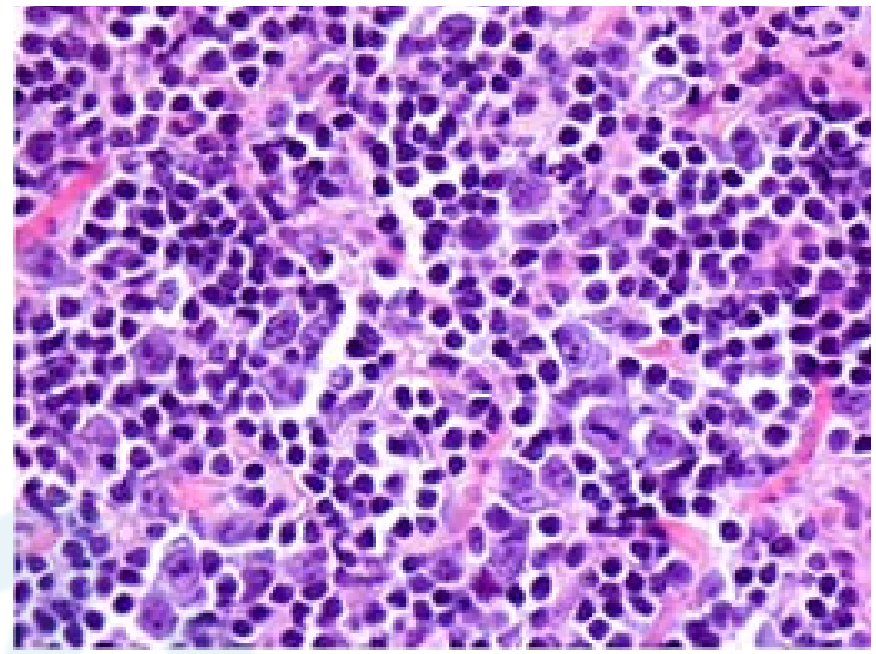
CD30



Ki67

Patient 3: last biopsy





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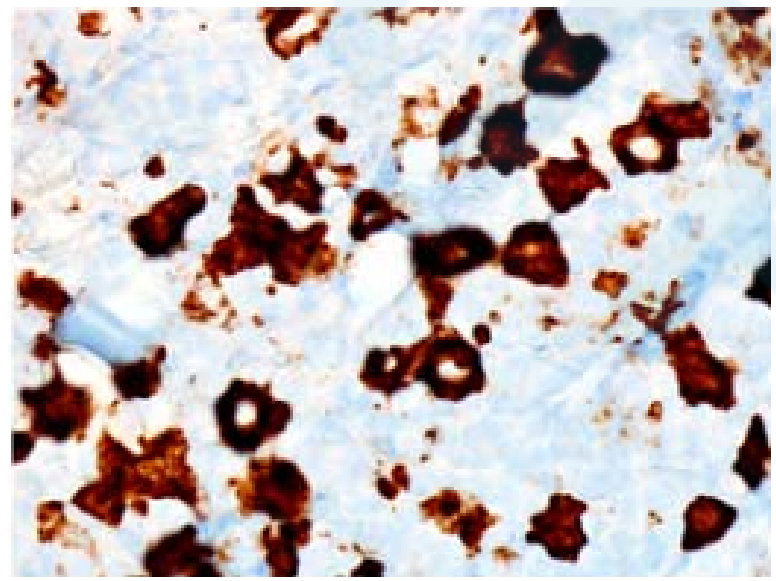
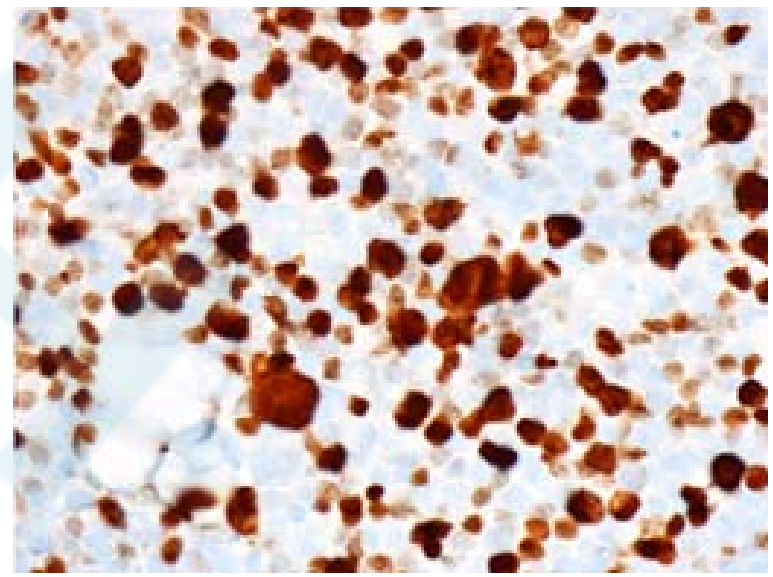
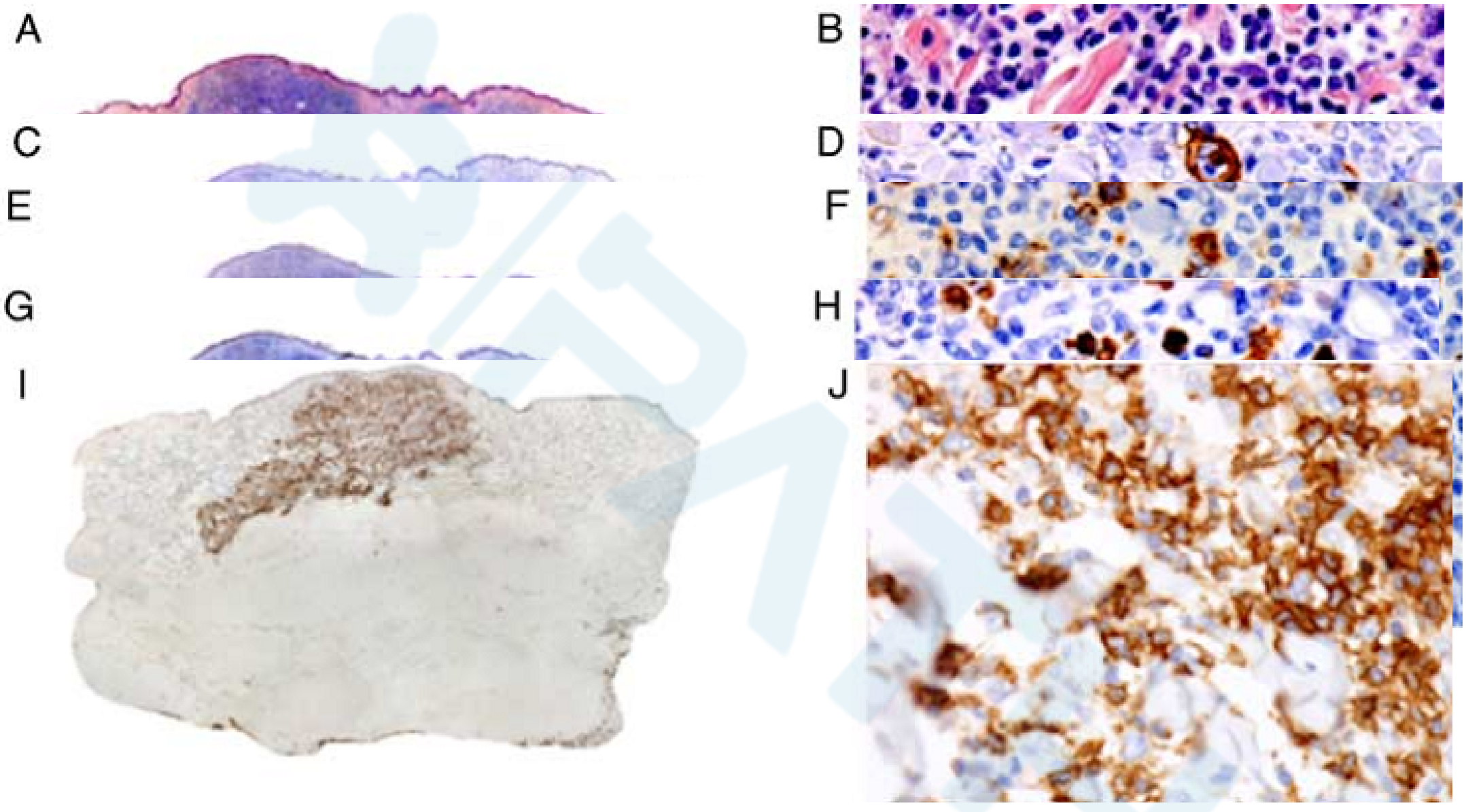


CD30

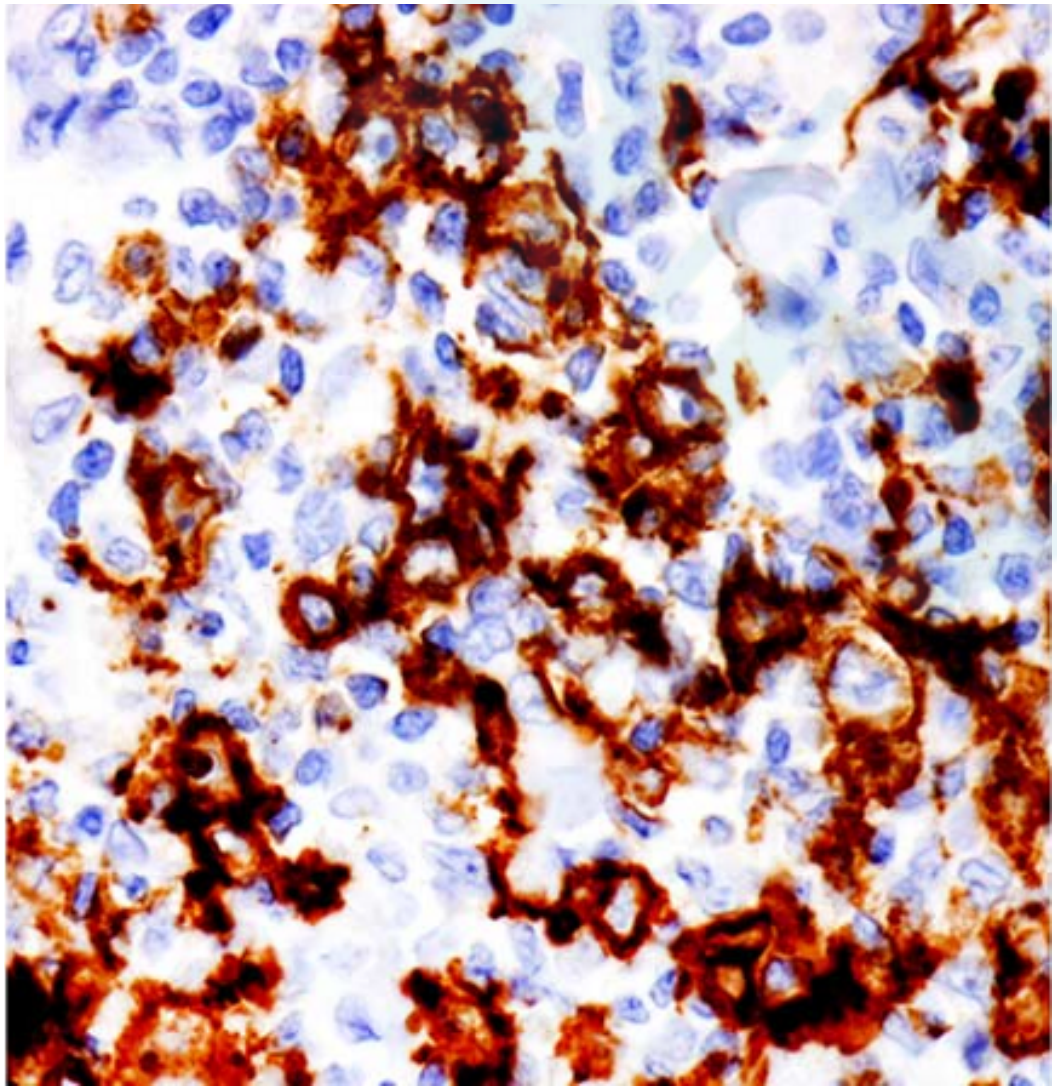


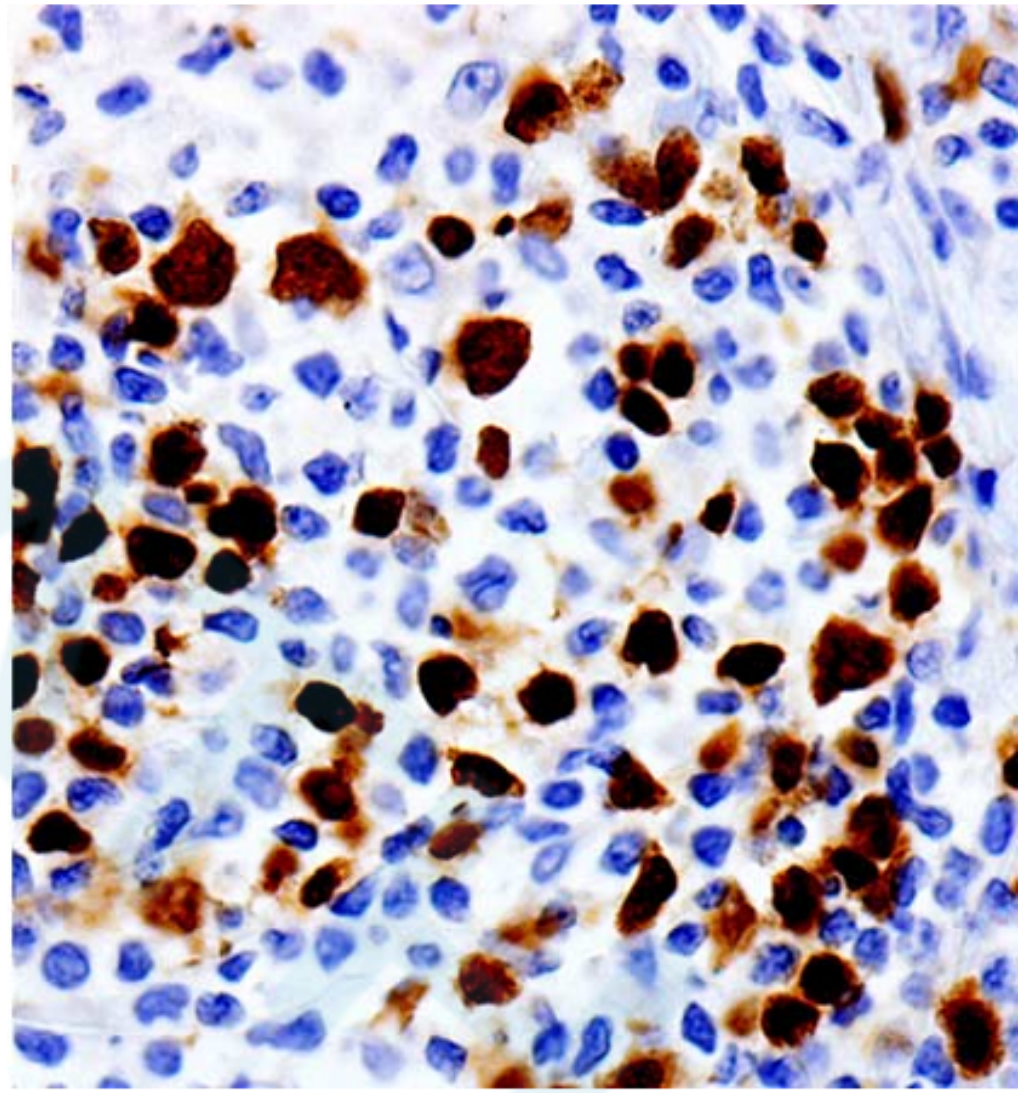
Ki67

Case 11: final biopsy



Case 11





The CD30+ and CD15+ large cells were also strongly positive for Pax5 and CD20.

TABLE 2. Main Histologic Features of the Cases

Case	Growth Pattern	Tumor Infiltrate	Reactive Follicles	Inflammatory Background	Presence of Large Cells (%)	$CD30^+$ Cells: Distribution and %	Reed-Sternberg or Hodgkin-like Cells	Epithelio-tropism
1	N	Mostly B and plasma cells	P	T	10-15	10, I	P	A
2	N	Mostly B and plasma cells	P	T	10-15	10, I	P	A
3	D	Mostly B	A*	T	40-50	40, D	P	A
4	N	Mostly B	P	T Rosettes around CD30 cells	30	30, I, D	P	A
5	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	20-30	10, I	P	A
6	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	20	10, I	P	A
7	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	10	10, I	P	A
8	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	20	15, I	P	A
9	N	Mostly B and plasma cells	P	T	20	15, I	P	A
10	N, M	Mostly B and plasma cells	A*	T Rosettes around CD30 cells	10	10, I	P	A
11	D	B cells	A*	T Rosettes around CD30 cells	30	15, I, D	P	A
12	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	20	15, I	P	A
13	N	Mostly B and plasma cells	P	T Rosettes around CD30 cells	30	30, I, D	P	A

A* indicates absent but with disrupted follicular structures; D, diffuse; I, interstitial; M, mixed; N, nodular; P, present.

TABLE 3. Main Immunophenotypic Features of Tumoral Cells and Companion Infiltrates

Case	CD20	CD30	CD15	Pax5	EBER	p53	Ki67 (%)	Bcl6	MYC	Bcl2	pSTAT3	CD123 CELLS	Light Chain Restriction	Dominant Plasma Cell Heavy Chain
1	+	+ in large cells	−	+	−	−	20	−	+ in some scattered large cells	+	−	Present clusters	Lamda	IgG
2	+	+	−	+	−	−	20	−	+ in some scattered large cells	+	Scattered	Scattered	Kappa	IgM
3	+	+	−	+	−	+ Scattered	50	−	NP	+	NP	NP	Kappa	IgM
4	+	+	−	+	−	−	20-30	−	+ in some scattered large cells	+	−	Present, clusters	Kappa	IgG-IgG4
5	+	+	−	+	−	−	20-30	−	+ in some scattered large cells	+	−	Present, clusters	No restriction	No plasma cells
6	+	+	−	+	−	−	20	−	+ in some scattered large cells	+	−	Clusters around vessels	Lambda	IgM
7	+	+	−	+	−	−	20	−	+ in some scattered large cells	+	−	Clusters around vessels	Kappa	IgM (Myd88 not mutated)
8	+	+	−	+	−	−	30	−	+ in some scattered large cells	+	−	Clusters around vessels	Kappa	IgG
9	+	+	−	+	−	−	20	−	+ in some scattered large cells	+	−	Clusters around vessels	Kappa	IgG4 Myd88 mutated
10	+	+	−	+	−	−	30	−	+ in some scattered large cells	+	−	Clusters around vessels	Lambda	IgG
11	+	+	+	+	−	+ Scattered	30	−	+ in some scattered large cells	+	−	Clusters around vessels	None	No plasma cells present
12	+	+	−	+	−	−	30	−	+ in some scattered large cells	+	−	Clusters around vessels	Lambda	IgG
13	+	+	−	+	−	−	30	−	+ in large cells, in follicles	+	−	Absent	Kappa	IgG

RESULTS

- No significant difference in percentage of CD30+ cells depending on the presence or absence of relapses.
- Patients with >15% of CD30+ cells compared with those with 10%: more relapses.

- Ki67: low or intermediate, 20-50%; progressed samples with a higher proportion.

RESULTS

TCR and IgH Gene Rearrangements

- All cases: clonal rearrangement of IgH and/or light chains; same clonal peak but case 12.
- 7 cases: TCR gamma, beta clonal rearrangement;

  Cases with more atypical PD1+ T-cell: T-cell monoclonal rearrangement.

Other Genotypic Studies (7 cases; NGS)

- Case 3 : *KMT2D*-R5048L and *KMT2D*-C349W (MLL2);
- Cases 1 and 11: *NOTCH2*-A3F mutation;
- Case 9: NFKBIE mutation and *MYD88* L265P;
- Cases 4, 6, and 8 were wild type.

DISCUSSION

- PCMZL series: scattered large neoplastic cells.
- Rodríguez-Pinilla *et al :* CD30+ large lymphoid cells surrounded by PD1+ cells.
- In our series: CD30+ cells in the reactive follicles of PCMZL, more diffuse distribution of CD30+ large cells outside the reactive follicles and surrounded by PD1+ T cells.
- Cases 3 and 11:

  CD30+ large cells associated with histological transformation and clinical progression;

  Higher frequency of relapses with a higher frequency of CD30+ cells

DISCUSSION

- PD1+ T-cell rosettes:
  TCR-gamma and TCR-beta clonality;
  PCMZL and other B-cell lymphomas.
- Presence of PD1-expressing T cells:

1. Goyal *et al* :

PD1:CD3+ T cells ratio: 17% to 34% in 6 PCMZLs, lower values than reactive processes.

2. Edinger *et al :*

Lower proportion (<10%) of PD1+ cells in PCMZL *vs* primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder (20% ~ 30%)

DISCUSSION

- Presence of CD30+ large cells with immunoblast or Hodgkin-like morphology surrounded by rosettes of atypical T cells: rule out a systemic HL.
- Primary cutaneous HL does not exist:

1.The rare cutaneous Hodgkin lymphoma:

secondary to systemic disease;

2. Most reported primary cutaneous HL:

actually other cutaneous lymphomas with Hodgkin-like features (lymphomatoid papulosis, primary cutaneous ALCL or PCMZL with Hodgkin-like cells).

DISCUSSION

- Few series of PCMZL have been studied the relapse rate and disease-free survival.
- One of the largest series (137 patients, Servitje *et al.*):

  1. Multifocal lesions or T3 disease: related to a higher relapse rate and shorter DFS.
  2. Similarties: male predominant, trunk and extremities, EORTC/ISCL staging system.
  3. Differences: 51% T1, 44% relapse; in our series (high proportion of large CD30+ cells), only 31% T1, higher relapse (69%).

- Our series: significant relationship between high frequencies of CD30+ cells and the clinical progression of the disease.

Conclusion

- Presence of neoplastic large CD30+ cells:

  1. Not unusual in PCMZL, associated with PD1+ T-cell rosettes.

  2. More aggressive behavior, with multiple recurrences in different locations and large tumor masses.

- Suggestion:

  1. CD30 should be added to the IHC panel;
  2. CD30 is a good marker for predicting lesions to recur;
  3. Full clinical and histopathologic study is necessary for differentiating PCMZL with Hodgkin lymphoma.

Thank You !