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Case Report

Metachronous Marginal Zone Lymphoma Followed by a Peripheral T-Cell Lymphoma in the Same Patient. Report of Two Cases and Review of the Literature

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Abstract

Marginal Zone Lymphomas (MZL) and Peripheral T Cell Lymphomas (PTCL) are uncommon neoplasms and patients affected by both lymphomas in a lifetime have been rarely reported. Here we present two patients with an initial diagnosis of a MZL who further developed a PTCL. We also present the review of the literature of six other cases of MZL. Half of the cases reported are synchronous and the other half metachronous. Most MZLs reported are MALT subtype. There is no predominant subtype amongst PTCLs. Chronic exposure to proinflammatory cytokines, genetic predisposition or exposure to carcinogenic agents could be possible causes underlying this rare phenomenon.

Keywords: Marginal zone lymphoma; Peripheral t-cell lymphoma; Synchronous; Metachronous

Case 1

A 45-year-old man with no previous medical records presented with asthenia in May 2014. Laboratory tests revealed iron-deficiency anemia. Serologies and autoimmunity tests including celiac disease study where negative. Thoracic-abdominal CT scan showed an enlargement of the first portion of the duodenum and enlarged mesenteric lymph nodes of 2cm. *Helicobacter Pilory* (HP) was negative. The duodenum biopsy showed a prominent lymphoid infiltrate involving the *lamina propia*. Immunohistochemistry markers were positive for B-cell and negative for CD3, CD5, CD10, BCL6 and cyclin D1. Ki67 index was <5%. IGH showed a clonal rearrangement. Bone marrow was not infiltrated. The diagnosis of Mucosa Associated Lymphoma Tissue (MALT) lymphoma stage II1E, with duodenal involvement was made. The patient received 3 cycles of R-CHOP achieving a complete response. In March 2016, he relapsed with multiple enlarged abdominal lymph nodes. Duodenum biopsy showed a MZL. TCR came out polyclonal. He received 4 cycles of Rituximab and Fludarabine, achieving a partial remission. On January 2018, he presented with abdominal pain. PET-CT scan showed an increased metabolic activity of the colon, and enlarged mesenteric lymph nodes (SUV max 17). Unfortunately, the patient presented rapid disease progression and died before a diagnostic biopsy could be performed. Necropsy showed a mesenteric mass also affecting the small bowel and right colon wall. Microscopically, it showed a diffuse infiltration of the serosa and the intestinal wall by medium-large cells that were positive for CD3, CD4, CD5, CD7, BF1 and cytotoxic markers (TIA and Granzyme B), and negative for CD8. CD30 was extensively positive especially in the larger cells. Ki67 index was 90%. B-cell markers, ALK and EBERs were negative. Molecular studies showed a clonal rearrangement of the TCR beta. IGH rearrangement was polyclonal. Differential diagnosis included ALK negative anaplastic large cell lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma, but morphologic and immunophenotypic analysis did not meet diagnostic criteria. Finally, a diagnosis of PTCL-NOS was made.

Case 2

A 62-year-old woman with no previous medical records presented with a right ocular mass and enlarged supraclavicular lymph nodes in October 2003. Blood tests were within normal ranges. Thoracic-abdominal CT scan showed no relevant findings. Lachrymal gland biopsy showed infiltration by MZL. Bone marrow was infiltrated. She was diagnosed with stage IVA MALT lymphoma and received Chlorambucil 2mg/day for a year with clinical resolution of both ocular mass and lymph nodes.

She remained uneventful until 2017, when she presented with a cervical enlarged lymph node. PET CT-scan showed supra- and infradiaphragmatic lymph nodes (SUVmax 12.5). Cervical lymph node biopsy was diagnostic of a PTCL, with T-follicular helper phenotype. EBERs was negative and TCR was clonal. B-cell markers and IGH rearrangement showed a small residual B-cell clonal population. She was started on CHOP chemotherapy, but after six cycles she presented with progressive disease. She was then treated with Bendamustine but had no response. She received salvage therapy with GEMOX, with progressive disease including multiple bones lesions. Unexpectedly, a biopsy of one of these lesions showed an aggressive B-cell lymphoma. Clonality studies showed that this lymphoma was related to the previous MALT lymphoma. The patient deceased shortly after the diagnosis.

Discussion

MZL and PTCL are rare neoplasms. The coexistence of both in the same patient cannot be explained by pure randomness, since the probability of these tumors is very low in our population. According

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Table 1: Clinical, pathologic, phenotipical and molecular features in 3 cases of synchronous MALT and T cell Lymphoma.

Case/Sex/Age/ Ref	Lymphoma 1						Lymphoma 2					
	Clinical presentation	Anatomical site	Morphology	IHC	Molecular tests	Diagnosis	Clinical presentation	Chronology & anatomical sites	Morphology	IHC/FC	Molecular tests	Diagnosis
4/F/68/2	B symptoms, toxic syndrome Md abdominal pain	Colon	Transmural small-medum hymphoid cells with small-medium cytoplasm, slightly irregular nucei	LCA+, CD20$^+$, CD79a. Pax5$^+$· Negative for T-cell markers	IGH clonal TCRG not clonal	MALT lymphoma	Breathing and swallng discomfort	2 years later, esophagus	infitration of the lamina propia by large lymphoid cells with irregular nuclei, prominent nuclecli, mitosis	CD3$^+$,CD4,CD56, CD8$^-$, CD30$^-$ "Negative for B-cell markers	TCRG clonal IGH clonal	PTCL, NOS
5/M/42/3	Toxic syndrome and abdominal pain	Stomach and bone marrow	n/d	CD20$^+$, CD5$^+$, CD38$^+$, K$^-$ LC CD10$^-$. cyclin D1$^-$	n/d	MALT lymphoma	n/d	6 months later, bone marrow	n/d	2 populations; 1. T-cells: CD8$^+$, CD3$^+$, CD5$^+$, CD7$^+$, CD45$^+$, 2. B-cells: CD19, CD79b, CD20, CD22,lgM, kappa LC	n/d	1. MALT lymphoma 2. T-LGL
6/?/?/4	n/d	esophagus	n/d	n/d	n/d	MALT lymphoma	Bowel perforation	9 years later, ileum	Dual population of medium-sized and a few large lymphoid cells	CD3$^+$,CD20$^-$, CD5$^-$,CD56$^+$, CD4$^+$,CD8$^-$. CD30$^+$ (in the papulation of larger cells).TIA-1 and granzyme B.	n/d	EATL, type II

IHC: Immunohistochemistry; FC: Flow Citometry; LC: Light Chain; ETL: Enteropathy-Type T Cell Lymphoma; EATL: Enteropathy-Associated T-Cell Lymphoma; MALT L: MALT Lymphoma; MZL: Marginal Zone Lymphoma; CHL: Classical Hodgkin Lymphoma; PTCL: Peripheral T Cell Lymphoma; ND: Not Described, TCRG: T-Cell Receptor Gamma; HRS: Hodgkin Reen-Sternberg Cells; Ref: Reference Number.

Table 2: Clinical, pathologic, phenotipical and molecular features in 3 cases of metachronous MALT and T cell Lymphoma.

Case/Sex/Age/ Ref	Clinical Presentation	Anatomical sites	Marginal Zone lymphoma				T-cell lymphoma			
			Morphology	IHC	Molecular tests	Diagnosis	Morphology	IHC	Molecular tests	Diagnosis
1/F/64/5	Incidental finding of gastric nodule inan endosoopy	Stomach	Small cells infiltrating the lamina propia with round or mildly irregular nuclei	CD20$^+$	IGH clonal	MALT lymphoma	Smalllymphocytes with mild atypia infitrating the surface and glandular epitelium	CD3$^+$,CD8$^+$, TIA-1+	TCRGdonal	Ell.
3/F/65/6	Cutaneous nodules (foream and leg), enlarged cervical and retroperitioneal lymph nodes	Skin: MZL + PTCL Cervical lymph node: cHL + PTCL	SKIN -Sheets of lymphoid cells with small indeded nuclei mixed with plasma cells infitrating deep dermis and subcutaneous tissue ˚T-cells: n/d	·C020$^+$	IGH clonal (skin)	Primary cutaneous marginal zone B cell lymphoma	LN: ·HRS cells ˚T-cells: n/d	LN & SKIN: T cells: CD3$^+$, CD4$^+$, TCRB negative	TCRGdonal (Skin and LN)	PTCL,NOS
2/F/57/7	Multiple lung/pleural lesions	Lung and pleura	Nodular infitrate os small-intermediate lymphocytes within the lung parenchima	CD20$^+$, C079a$^+$, BCL2$^+$,CD5$^-$, cyclin D1, CD23$^-$, BCL6$^-$ CD10$^-$	IGH clonal	MALT lymphoma	Large cells with plemorphic nuclei and abundant eosinophilic cytoplasm in pleural area	CD30$^+$,CD8$^+$, CD2$^+$, CD3w, CD7+/-, CD5$^-$, CD15$^-$,ALK1$^-$	TCRG clonal	ALCL, ALK negative

IHC: Immunohistochemistry; FC: Flow Citometry; LC: Light Chain; ETL: Enteropathy-Type T Cell Lymphoma; EATL: Enteropathy-Associated T-Cell Lymphoma; MALT L: MALT Lymphoma; MZL: Marginal Zone Lymphoma; CHL: Classical Hodgkin Lymphoma; PTCL: Peripheral T Cell Lymphoma; ND: Not Described, TCRG: T-Cell Receptor Gamma; HRS: Hodgkin Reen-Sternberg Cells; Ref: Reference Number.

to local registries [1], Marginal Zone Lymphomas and T/NK-cell lymphomas have an incidence of 2.59 and 2.01/100.000/year, respectively. In our area, the chances of developing both neoplasms within a 15 year-period of time are approximately 0.000012%. To our knowledge, only six cases of MZL and PTCL occurring in the same patient have been reported before in the literature [2-7]. The characteristics of these patients are summarized in (Table 1) (synchronous) and (Table 2) (metachronous).

Four possible explanations for the development of B and T-cell neoplasms in the same patient were posed by Medeiros and Stetler-Stevenson in 1992 [8]: First, that there might be a common stem cell precursor with the capacity to differentiate into a B- or T-cell tumor. Secondly, there could be an underlying genetic predisposition given by the activation of oncogenes or alterations in tumor suppressor genes. Third, previous exposure to a common carcinogen could independently transform B and T precursors. And fourth, the neoplastic B-cells secrete various cytokines that might chronically stimulate T-cells, leading to the development of small clones of T cells that might eventually transform into an aggressive lymphoma.

Other known factors associated with lymphomagenesis of MALT lymphomas are autoimmune disorders and chronic infections, but these have not been related to PTCLs [9]. Acquired immunodeficiencies caused by infectious agents or by previous cytotoxic treatments could play a role in the emergence of a second lymphoma. Also, Epstein Barr Virus (EBV) in immunosuppressed patients has the ability to induce a malignant transformation of normal B-cells [10], and these

cells may stimulate a T-cell proliferation that might become clonal through a process of clonal selection. However, none of our patients was positive for EBV.

In our first case, chronic exposure to proinflammatory cytokines secreted by MALT lymphoma could have locally stimulated T-cell proliferation that at a point became clonal and eventually transformed into a PTCL. This theory is reinforced by the fact that the MALT lymphoma relapsed or responded partially to different treatments, being this proinflammatory state sustained and also by the fact that PTCL appeared in the same site as the MALT lymphoma.

Regarding the second case, a genetic predisposition or an exposure to a common carcinogenic agent could explain the fact that she developed two different lymphomas. In summary, coexistence of MALT lymphomas and PTCL is extremely rare and the exact mechanisms underlying this phenomenon are yet to be elucidated. It is important to re-biopsy all the relapses of MALT lymphomas, in order to properly diagnose and treat the lymphoma. Further genetic or epigenetic studies could help us explain this co-existence in the future.

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References

1. Solans M, Fabrega A, Morea D, Aunon-Sanz C, Granada I, Roncero J, et al. Population-based incidence of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain. Cancer Epidemiology. 2019; 58: 8-11.
2. Venizelos J, Papadopoulos N, Lambropoulou M, Nikolaidou S, Bolioti S, Tamiolakis D. Metachronous Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma) and Peripheral T-Cell Lymphoma Unspecified: Histologic, Immunophenotypic, and Molecular Documentation. Oncology Research and Treatment. 2005; 28: 423-426.
3. Akoum R, Serhal W, Farhat H. Disseminated Gastric MALT Lymphoma with Monoclonal Gammopathy, t(11;18)(q21;q21), and Subsequent Development of T-Large Granular Lymphocytic Leukemia: A Case Report and Review of the Literature. Case Reports in Medicine. 2015.
4. Fonseca F, Meenal H, Bijal K. Discordant and metachronous Non-Hodgkin's lymphomas: Enteropathy-associated T-cell lymphoma, Type II with aberrant expression of CD4 presenting several years after a mucosa-associated lymphoid tissue type B-cell lymphoma. Indian Journal of Pathology and Microbiology. 2015; 58: 569-570.
5. Yun W, Ko Y, Kim D, Kim W, Rhee P, Kwak S, et al. Composite marginal zone B cell lymphoma and enteropathy-type T cell lymphoma of the stomach: a case report. European Journal of Gastroenterology & Hepatology. 2008; 20: 791-795.
6. Steinhoff M, Assaf C, Anagnostopoulos I, Geilen C, Stein H, Hummel M. Three coexisting lymphomas in one patient: genetically related or only a coincidence?. Journal of Clinical Pathology. 2006; 59: 1312-1315.
7. Wang E, Papavassiliou P, Wang A, Louissaint A, Wang J, Hutchinson C, et al. Composite lymphoid neoplasm of B-cell and T-cell origins: a pathologic study of 14 cases. Human Pathology. 2014; 45: 768-784.
8. Medeiros L, Stetler-Stevenson M. Composite B-Cell and T-Cell Lymphoma: Coincidental Occurrence or Related Neoplasms?. American Journal of Clinical Pathology. 1992; 98: 387-389.
9. Chihara D, Nastoupil L, Williams J, Lee P, Koff J, Flowers C. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy. Expert Review of Anticancer Therapy. 2015; 15: 531-544.
10. Grywalska E, Rolinski J. Epstein-Barr Virus–Associated Lymphomas. Seminars in Oncology. 2015; 42: 291-303.