Linfomi B della zona marginale

Marco Paulli

Anatomia Patologica

Dipartimento di Medicina Molecolare

Universita' di Pavia e Fondazione IRCCS Policlinico San Matteo

La storia

1959 Lennert: sinusoidal histiocytes

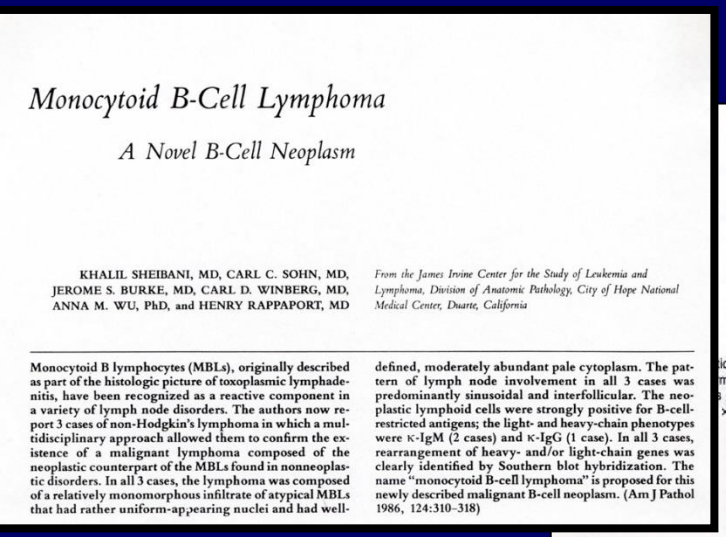
1961 Stansfeld: monocytoid cells

1984 De Almeda: large sinus lymphocytes

1984 Sheibani: monocytoid B lymphocytes

1984 Isaacson: MALT lymphoma

1986 Sheibani: monocytoid B cell lymphoma



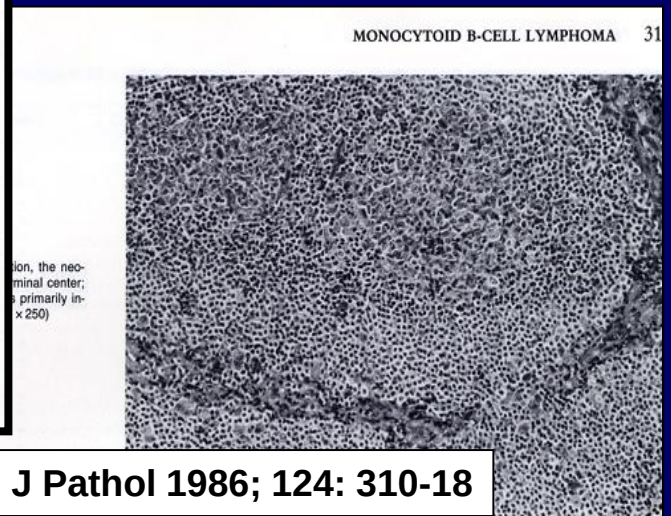
Monocytoid B-Cell Lymphoma

A Novel B-Cell Neoplasm

KHALIL SHEIBANI, MD, CARL C. SOHN, MD, JEROME S. BURKE, MD, CARL D. WINBERG, MD, ANNA M. WU, PhD, and HENRY RAPPAPORT, MD

From the James Irvine Center for the Study of Leukemia and Lymphoma, Division of Anatomic Pathology, City of Hope National Medical Center, Duarte, California

Monocytoid B lymphocytes (MBLs), originally described as part of the histologic picture of toxoplasmic lymphadenitis, have been recognized as a reactive component in a variety of lymph node disorders. The authors now report 3 cases of non-Hodgkin's lymphoma in which a multidisciplinary approach allowed them to confirm the existence of a malignant lymphoma composed of the neoplastic counterpart of the MBLs found in nonneoplastic disorders. In all 3 cases, the lymphoma was composed of a relatively monomorphous infiltrate of atypical MBLs that had rather uniform-appearing nuclei and had well-defined, moderately abundant pale cytoplasm. The pattern of lymph node involvement in all 3 cases was predominantly sinusoidal and interfollicular. The neoplastic lymphoid cells were strongly positive for B-cell-restricted antigens; the light- and heavy-chain phenotypes were κ-IgM (2 cases) and κ-IgG (1 case). In all 3 cases, rearrangement of heavy- and/or light-chain genes was clearly identified by Southern blot hybridization. The name "monocytoid B-cell lymphoma" is proposed for this newly described malignant B-cell neoplasm. (Am J Pathol 1986, 124:310–318)



MONOCYTOID B-CELL LYMPHOMA 31

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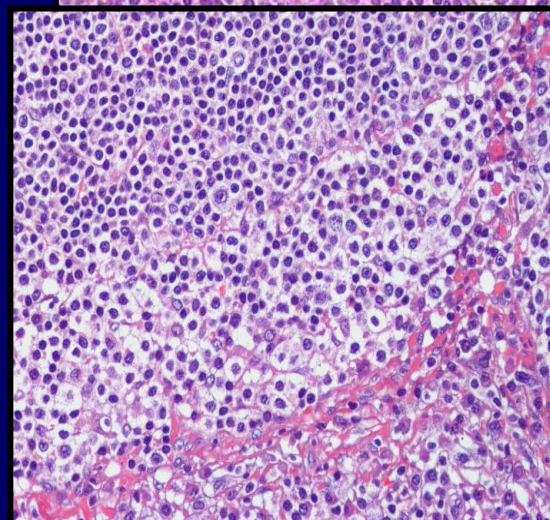
Am J Pathol 1986; 124: 310-18

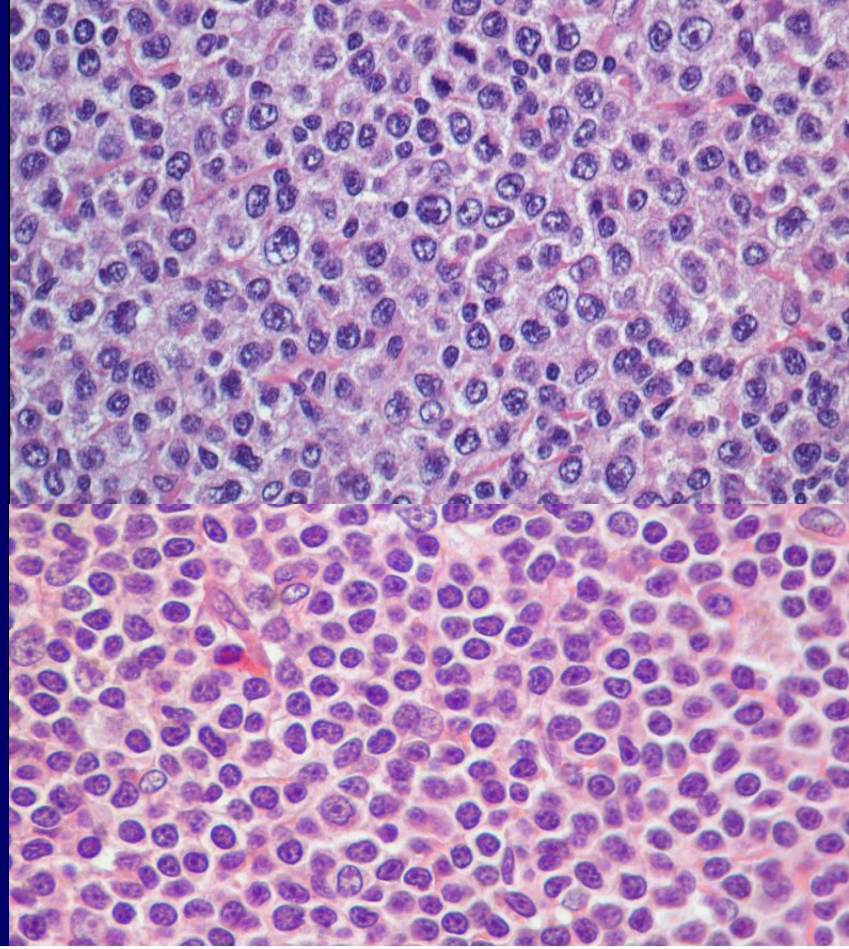


LNH Monocitoide: 2 varianti

I- medie cellule simil-monocitoidi, discreto citoplasma chiaro, nuclei tondi-ovalari, nucleoli singoli; “pattern” sinusale

II- piccole cellule simil-centroidi; citoplasma scarso non basofilo; “pattern” marginale

N.B.: *“Since we noticed a case containing both a medium sized and small cell component, we are not presently able to sharp distinguish between the two variants”*



Monocytoid B-cell lymphoma: morphological variants and relationship to low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue

H.NIZZE*, S.B.COGLIATTI, C.VON SCHILLING, A.C.FELLER & K.LENNERT
*Departments of Pathology, University of Kiel, and *University of Rostock, Germany*

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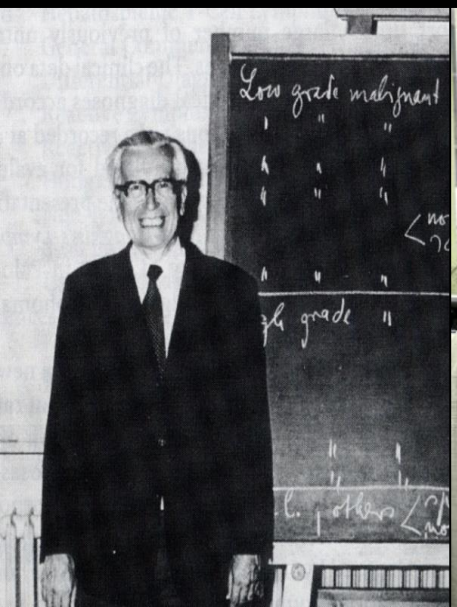
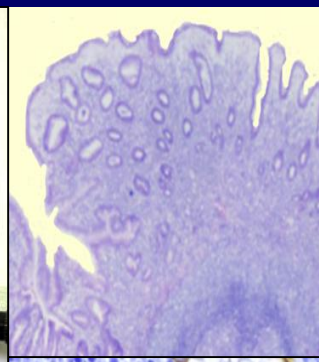
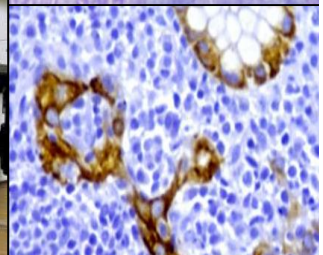
NIZZE H., COGLIATTI S.B., VON SCHILLING C., FELLER A.C. & LENNERT K.
(1991) *Histopathology* 18, 403–414

La Kiel 1988 colloca il MBCL prima tra le forme rare, ma in seguito resisi conto trattarsi di forma non così rara, lo inserisce (“up-date 92”) tra LNH B di basso grado, includendo anche il linfoma della zona marginale; compare anche, in addendum, il linfoma MALT-type







Updated Kiel classification of non-Hodgki

B

Low-grade malignant lymphomas

Lymphocytic
Chronic lymphocytic leukaemia
Prolymphocytic leukaemia

Hairy-cell leukaemia

Lymphoplasmacytic/-cytoid (immunocyton

Plasmacytic

Centroblastic-centrocytic
follicular ± diffuse
diffuse

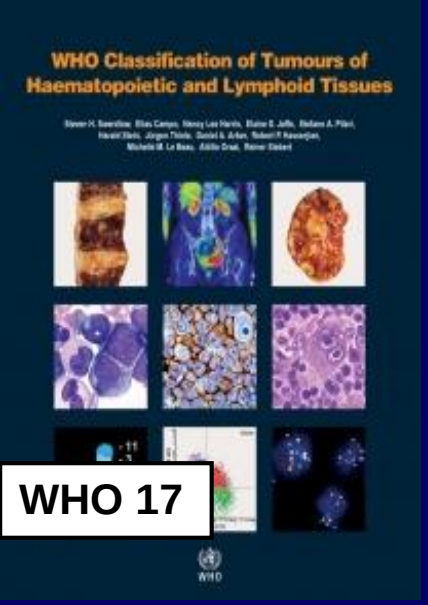
Centrocytic (mantle cell)

Monocytoid, including marginal zone cell

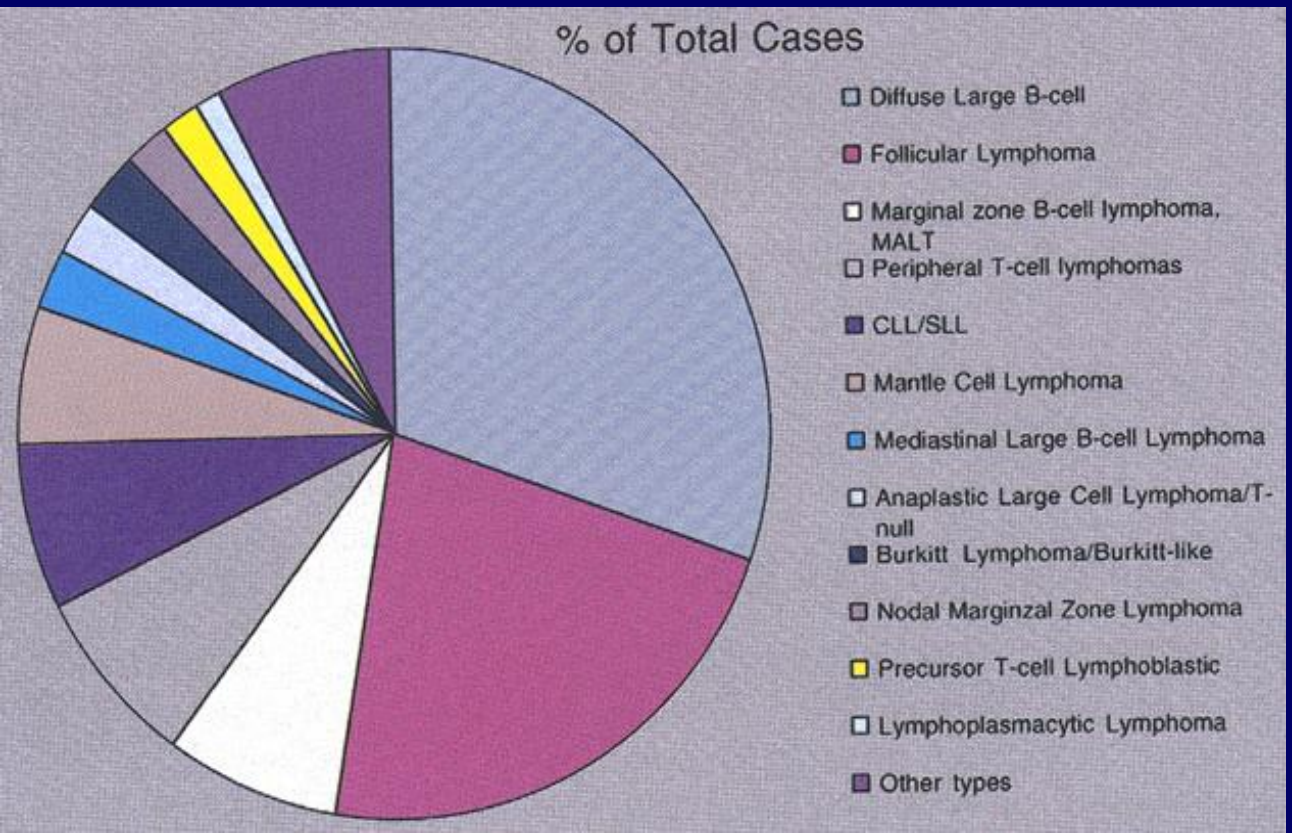
High-grade malignant lymphomas

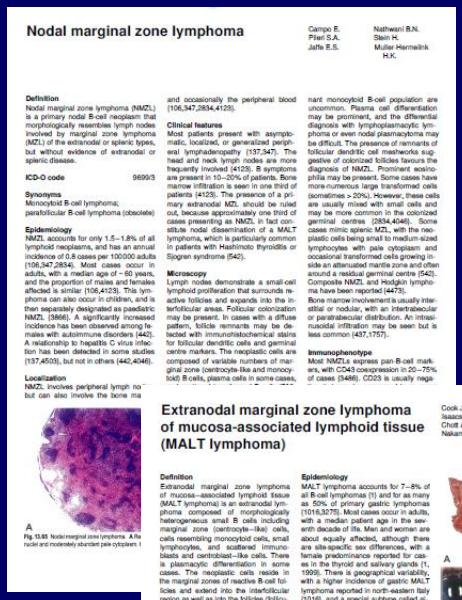
Centroblastic

Immunoblastic



- Primary Nodal MZL **(1.5-1.8% LNH)**
- Primary Splenic MZL **(<2% LNH)**
- Extranodal MZL MALT-type **(7.8 % LNH)**





Nodal marginal zone lymphoma

Campo E. Pileri S.A. Jaffe E.S. Nathwani B.N. Stein H. Muller-Hermelink H.K.

Definition
Nodal marginal zone lymphoma (NMZL) is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by marginal zone lymphoma (MZL) of the extranodal or splenic types, but without evidence of extranodal or splenic disease.

ICD-O code 9699/3

Synonyms
Monocytoid B-cell lymphoma; parafollicular B-cell lymphoma (obsolete)

Epidemiology
NMZL accounts for only 1.5–1.8% of all lymphoid neoplasms, and has an annual incidence of 0.8 cases per 100000 adults (106,347,2834). Most cases occur in adults, with a median age of ~ 60 years, and the proportion of males and females affected is similar (106,4123). This lymphoma can also occur in children, and is then separately designated as paediatric NMZL (3866). A significantly increased incidence has been observed among females with autoimmune disorders (442). A relationship to hepatitis C virus infection has been detected in some studies (137,4503), but not in others (442,4046).

Localization
NMZL involves peripheral lymph no[des] but can also involve the bone ma[rrow] and occasionally the peripheral blood (106,347,2834,4123).

Clinical features
Most patients present with asymptomatic, localized, or generalized peripheral lymphadenopathy (137,347). The head and neck lymph nodes are more frequently involved (4123). B symptoms are present in 10–20% of patients. Bone marrow infiltration is seen in one third of patients (4123). The presence of a primary extranodal MZL should be ruled out, because approximately one third of cases presenting as NMZL in fact constitute nodal dissemination of a MALT lymphoma, which is particularly common in patients with Hashimoto thyroiditis or Sjogren syndrome (542).

Microscopy
Lymph nodes demonstrate a small-cell lymphoid proliferation that surrounds reactive follicles and expands into the interfollicular areas. Follicular colonization may be present. In cases with a diffuse pattern, follicle remnants may be detected with immunohistochemical stains for follicular dendritic cells and germinal centre markers. The neoplastic cells are composed of variable numbers of marginal zone (centrocyte-like and monocytoid) B cells, plasma cells in some cases, [nant] monocytoid B-cell population are uncommon. Plasma cell differentiation may be prominent, and the differential diagnosis with lymphoplasmacytic lymphoma or even nodal plasmacytoma may be difficult. The presence of remnants of follicular dendritic cell meshworks suggestive of colonized follicles favours the diagnosis of NMZL. Prominent eosinophilia may be present. Some cases have more numerous large transformed cells (somatimes > 20%). However, these cells are usually mixed with small cells and may be more common in the colonized germinal centres (2834,4046). Some cases mimic splenic MZL, with the neoplastic cells being small to medium-sized lymphocytes with pale cytoplasm and occasional transformed cells growing inside an attenuated mantle zone and often around a residual germinal centre (542). Composite NMZL and Hodgkin lymphoma have been reported (4473).
Bone marrow involvement is usually interstitial or nodular, with an interbecular or paratrabecular distribution. An intrasinusoidal infiltration may be seen but is less common (437,1757).

Immunophenotype
Most NMZLs express pan-B-cell markers, with CD43 coexpression in 20–75% of cases (5486). CD23 is usually nega-

A
Fig. 13.65 Nodal marginal zone lymphoma. A Re[active] nuclei and moderately abundant pale cytoplasm.

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Cook J.R. Isaacson P.G. Chott A. Nakamura S. Muller-Hermelink H.K. Harris N.L. Swerdlow S.H.

Definition
Extranodal marginal zone lymphoma of mucosa–associated lymphoid tissue (MALT lymphoma) is an extranodal lymphoma composed of morphologically heterogeneous small B cells including marginal zone (centrocyte–like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast–like cells. There is plasmacytic differentiation in some cases. The neoplastic cells reside in the marginal zones of reactive B-cell follicles and extend into the interfollicular region as well as into the follicles (follicular colonization). In epithelial tissues, the neoplastic cells typically infiltrate the epithelium, forming lymphoepithelial lesions (1044,1782). Thus, MALT lymphomas variably recapitulate Peyer's patch-type lymphoid tissue, the prototypical normal mucosa-associated lymphoid tissue (MALT). MALT lymphomas arising at any anatomical site share many characteristics, but there are also site-specific differences with respect to etiology, morphological features, molecular cytogenetic abnormalities, and clinical course (502, 1044,2140).

ICD-O code 9699/3

Epidemiology
MALT lymphoma accounts for 7–8% of all B-cell lymphomas (1) and for as many as 50% of primary gastric lymphomas (1016,3275). Most cases occur in adults, with a median patient age in the seventh decade of life. Men and women are about equally affected, although there are site-specific sex differences, with a female predominance reported for cases in the thyroid and salivary glands (1, 1999). There is geographical variability, with a higher incidence of gastric MALT lymphoma reported in north-eastern Italy (1016), and a special subtype called alpha heavy chain disease (also known as immunoproliferative small intestinal disease) occurs in the Middle East (48,4230), the Cape region of South Africa (3239), and a variety of other tropical and subtropical locations (see Alpha heavy chain disease, p. 240).

Etiology
In many MALT lymphoma cases, there is a history of a chronic inflammatory disorder that results in accumulation of extranodal lymphoid tissue (called acquired MALT). The chronic inflammation may be the result of infection, autoimmunity, or unknown other stimuli.
The link between infection and MALT lymphoma is most clearly established for Helicobacter pylori and gastric MALT

A

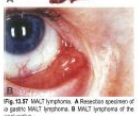


Fig. 13.57 MALT lymphoma. A Resection specimen of a gastric MALT lymphoma. B MALT lymphoma of the conjunctiva.

lymphoma (1199,3954). The continued proliferation of gastric MALT lymphoma cells from patients infected with H. pylori depends on the presence of T cells specifically activated by H. pylori antigens and/or direct oncogenic effects of H.pylori proteins on B cells (1741,2137). The importance of this stimulation in vivo has been clearly demonstrated by the

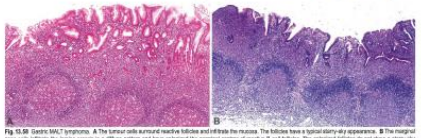


Fig. 13.58 Gastric MALT lymphoma. A The tumour cells surround reactive follicles and infiltrate the mucosa. The follicles have a typical starry-sky appearance. B The marginal zone cells infiltrate the lamina propria in a diffuse pattern and have colonized the germinal centres of reactive B-cell follicles. The colonized follicles do not show a starry-sky pattern.

MZL nodale

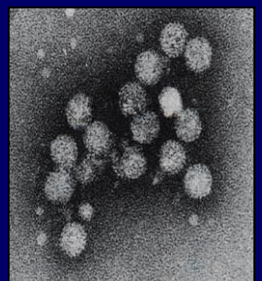
- F>M; V- VI decade; forma pediatrica (???)
- Associazione forme autoimmuni (Hashimoto e Sjogren) e HCV
- Linfonodi superficiali e profondi, midollo (30-40% pz), periferico
- Spesso stadio III-IV; sintomi B (10-20% pz); > LDH
- Escludere concomitanti lesioni sedi MALT!

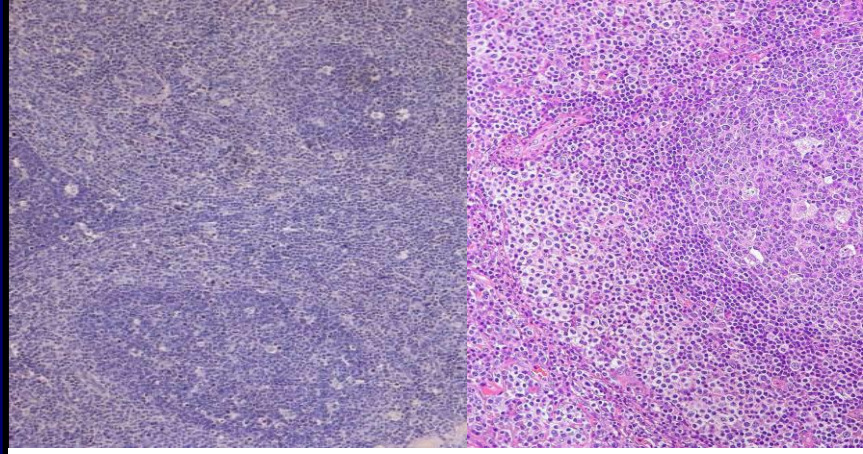
Splenic and Nodal Marginal Zone Lymphomas Are Indolent Disorders at High Hepatitis C Virus Seroprevalence with Distinct Presenting Features but Similar Morphologic and Phenotypic Profiles

Luca Arcaini, M.D.[1]
Marco Paulli, M.D.[2]
Emanuela Boveri, M.D.[2]
Daniele Vallisa, M.D.[3]
Patrizia Bernuzzi, M.D.[3]
Ester Orlandi, M.D.[1]

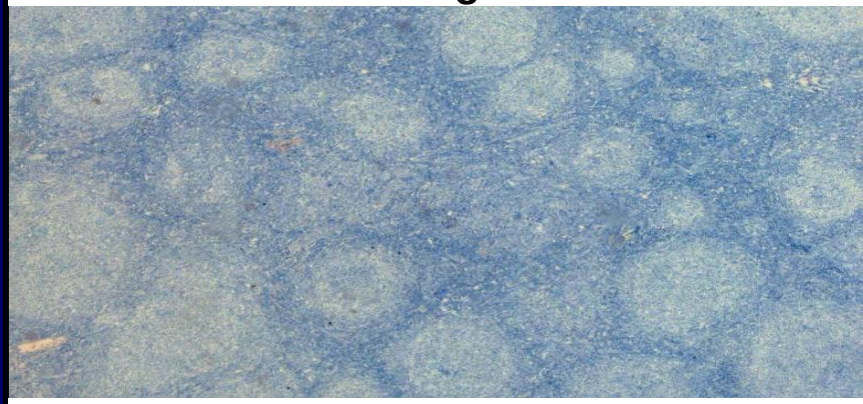
BACKGROUND. Splenic and nodal marginal zone lymphomas (MZL) are subtypes of marginal zone-derived neoplasms. Due to their rarity, little is known concerning their relation, pattern of dissemination, and treatment outcome.
METHODS. The authors analyzed the clinicopathologic features and outcome of 43 patients (34 patients with splenic MZL and 9 patients with nodal MZL). All lesional tissues obtained at diagnosis were reviewed histologically.

Arcaini L. Cancer. 2004 Jan 1;100(1):107 15

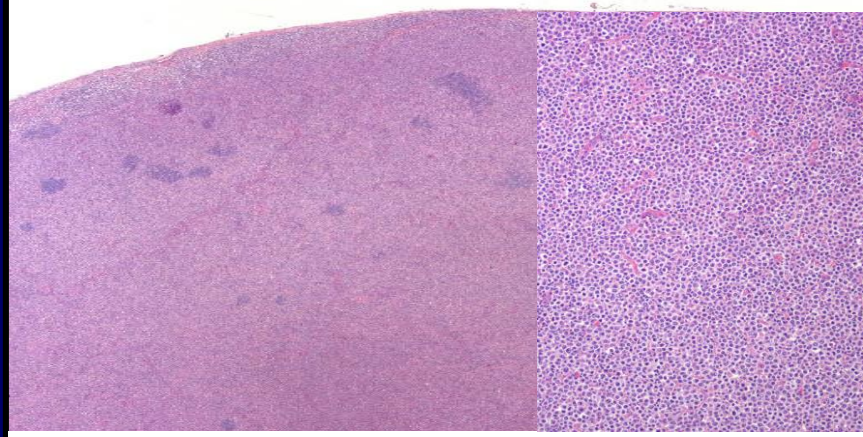




Pattern Sinusale-marginale



Pattern Nodulare

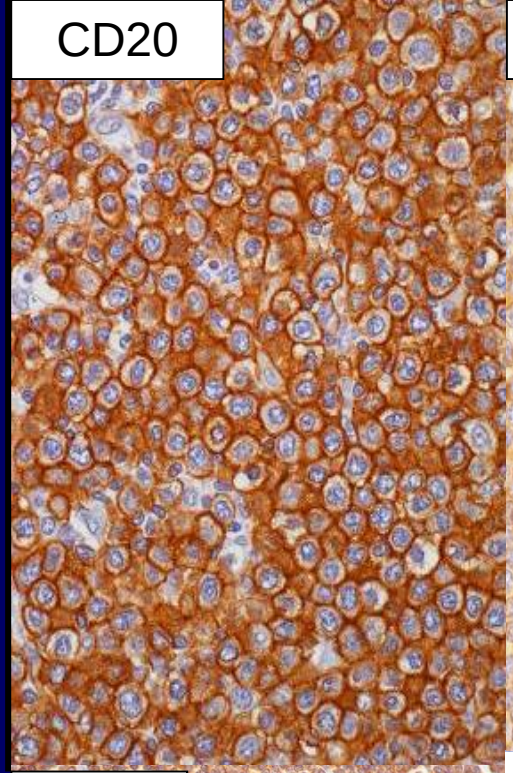


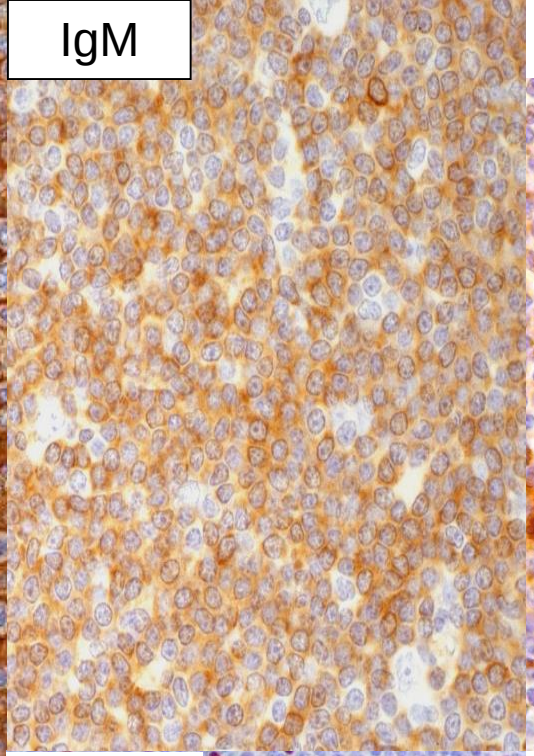
Pattern Diffuso

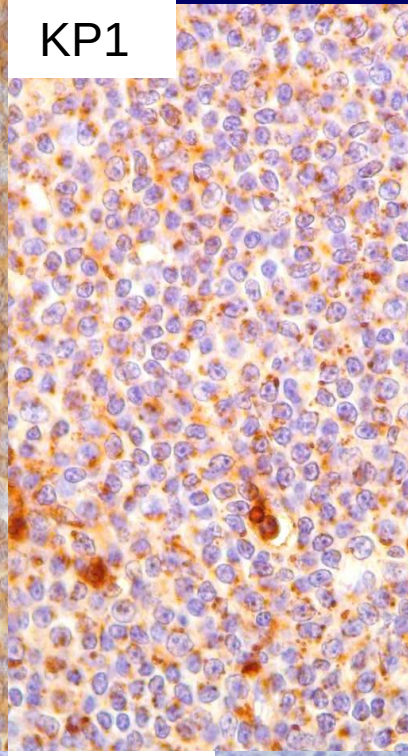
- CD20+
- CD10-
- CD79a+
- CD11c+/-
- IgM+
- CD5-/+*
- CD43+/-
- Bcl-1-
- TCL1-
- Bcl-2+/-
- KP1+/-
- CD23-/+**

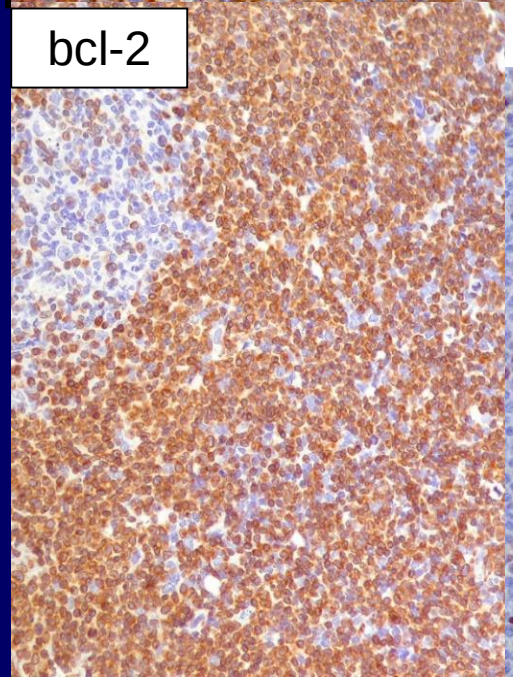
*(+ 29%)

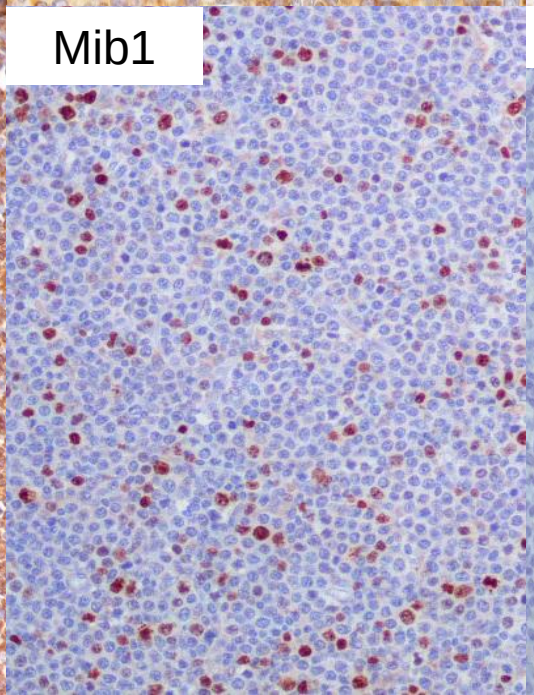
**(+17%)

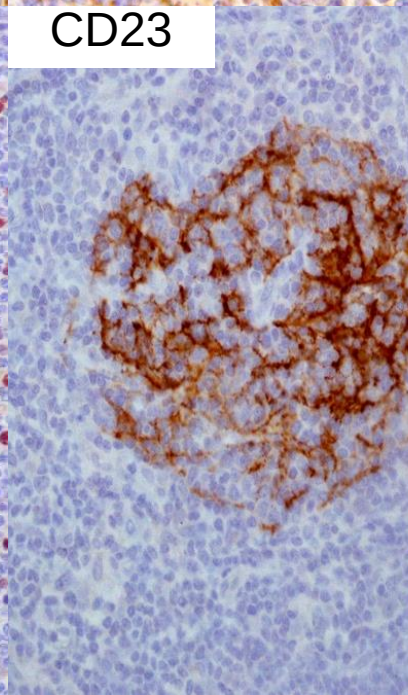






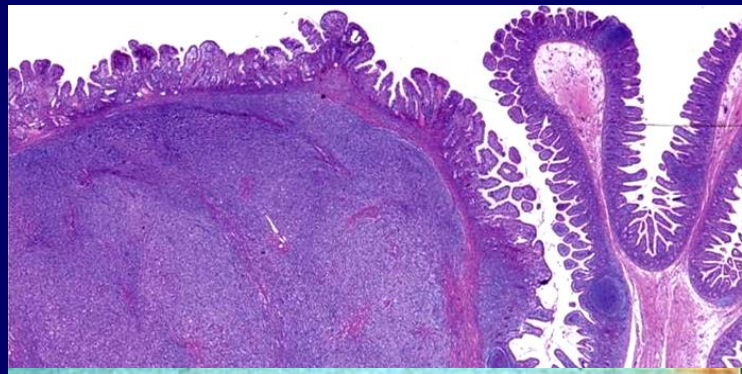


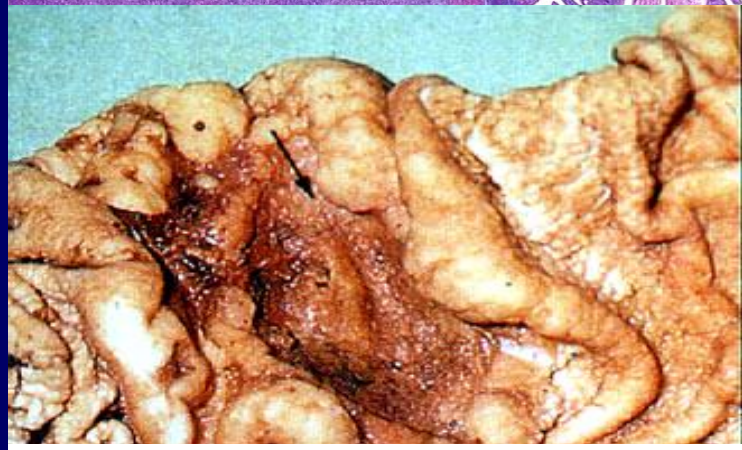


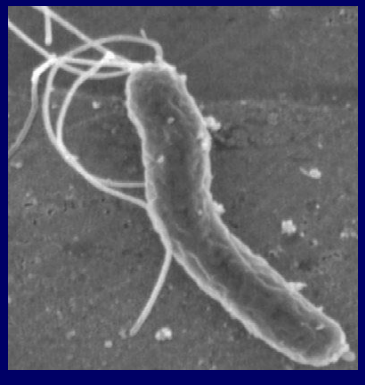


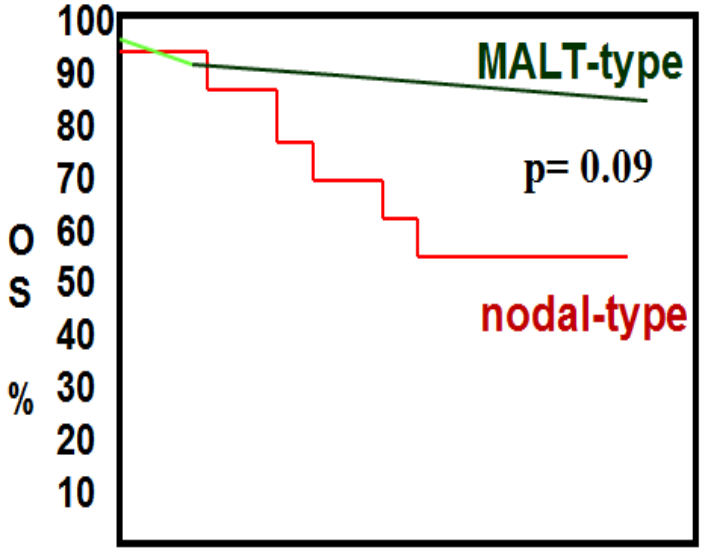
LZM extranodale MALT-type

- Media 63 anni; M=F;
- Spesso eziologia infettiva; concomitanti forme autoimmuni (Sjogren,Hashimoto)
- Stomaco (35%), annessi oculari (13%), cute (9%), polmoni (9%), salivari (8%), tiroide (2%)
- Stadio I/II 30-40% pz
- Indolenti: 80% a 10 anni; rischio disseminazione sede correlato (10% salivari, 17% stomaco, 44% polmone)





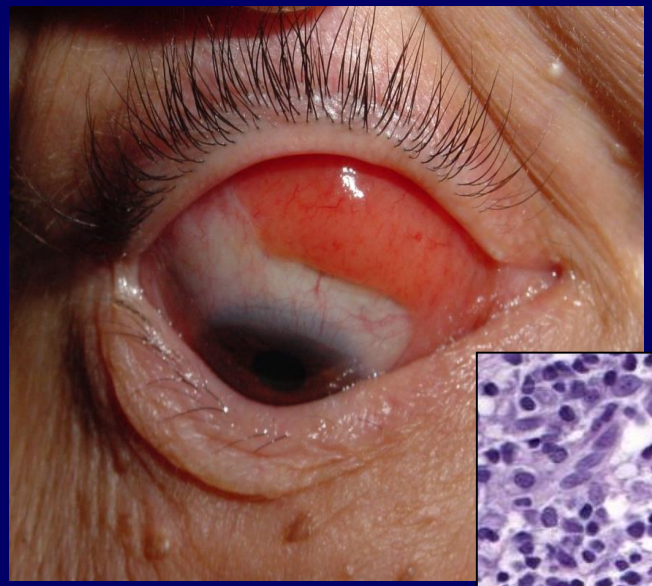


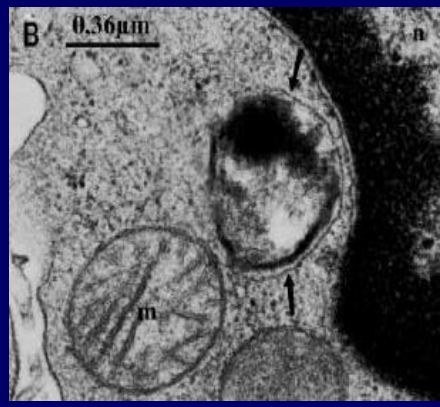


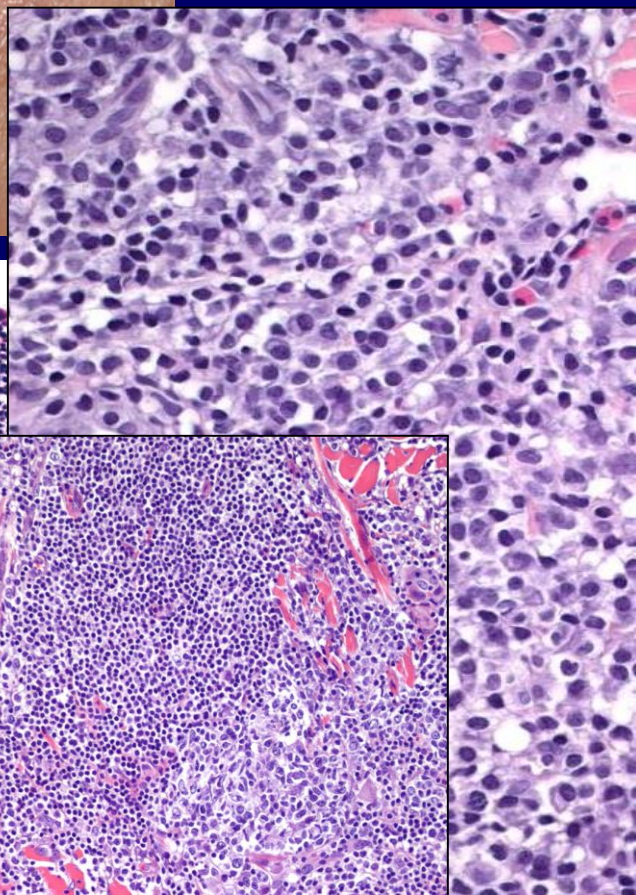
Marshall BJ & Warren JR. Unidentified curved bacilli on gastric epitheliu
in active chronic gastritis, *The Lancet* **1983; Nobel 2005**

Linfomi MALT annessi oculari

- 12% LZM MALT
- Congiuntiva, palpebra, ghiandola lacrimale, tessuti molli retro-orbitali
- Associazione con *Chlamydia psittaci* mostra significativa variabilità geografica: 80% dei casi in Italia
- Spesso regressione lesionale dopo terapia antibiotica

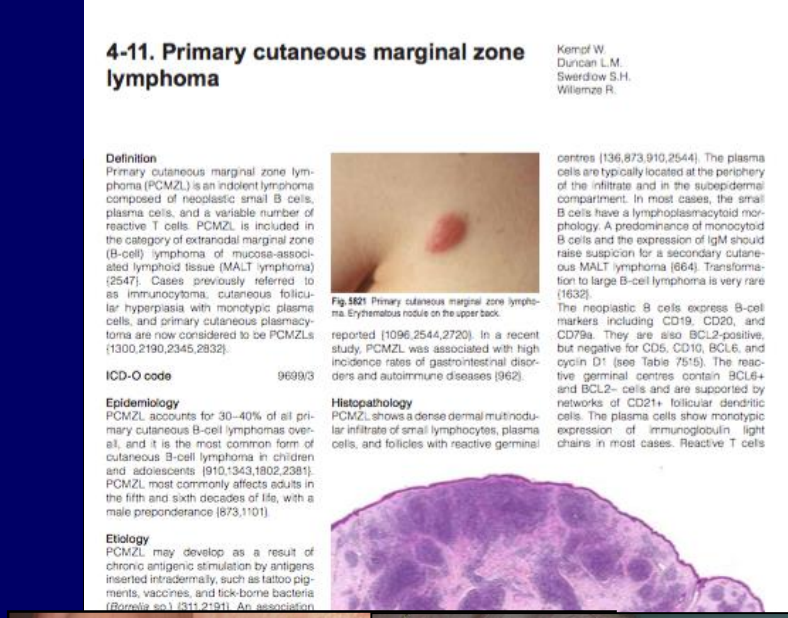






MZL primitivo cutaneo

- Immunocitomi, iperplasia follicolare cutanea con plasmacellule monotipiche, PC plasmocitomi, prima inclusi nei PC MZL
- 9% MALTomi extran.; 16- 40% PCBCLs; 5-6a decade, > M; casi pediatrici (???)
- Arti, testa e tronco; placche/noduli solitari/multipli, rosso-violacei; bordo eritematoso
- Talora “regressione spontanea; soprav. 95-100% a 5 anni
- Recidive 33-66% pz, prognosticamente ininfluenti
- Stadiazione estensiva ?



4-11. Primary cutaneous marginal zone lymphoma

Kempf W.
Duncan L.M.
Swerdlow S.H.
Willemze R.

Definition
Primary cutaneous marginal zone lymphoma (PCMZL) is an indolent lymphoma composed of neoplastic small B cells, plasma cells, and a variable number of reactive T cells. PCMZL is included in the category of extranodal marginal zone (B-cell) lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (2547). Cases previously referred to as immunocytoma, cutaneous follicular hyperplasia with monotypic plasma cells, and primary cutaneous plasmacytoma are now considered to be PCMZLs (1300,2190,2345,2832).

ICD-O code 9699/3

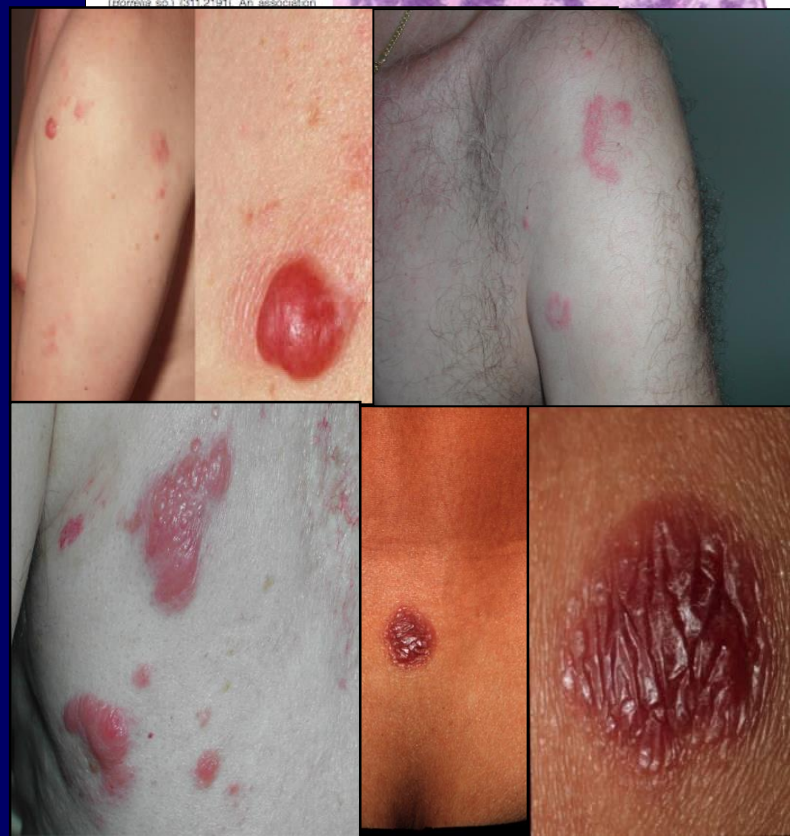
Epidemiology
PCMZL accounts for 30–40% of all primary cutaneous B-cell lymphomas overall, and it is the most common form of cutaneous B-cell lymphoma in children and adolescents (910,1343,1802,2381). PCMZL most commonly affects adults in the fifth and sixth decades of life, with a male preponderance (873,1101).

Etiology
PCMZL may develop as a result of chronic antigenic stimulation by antigens inserted intradermally, such as tattoo pigments, vaccines, and tick-borne bacteria (*Borrelia* sp.) (311,2191). An association

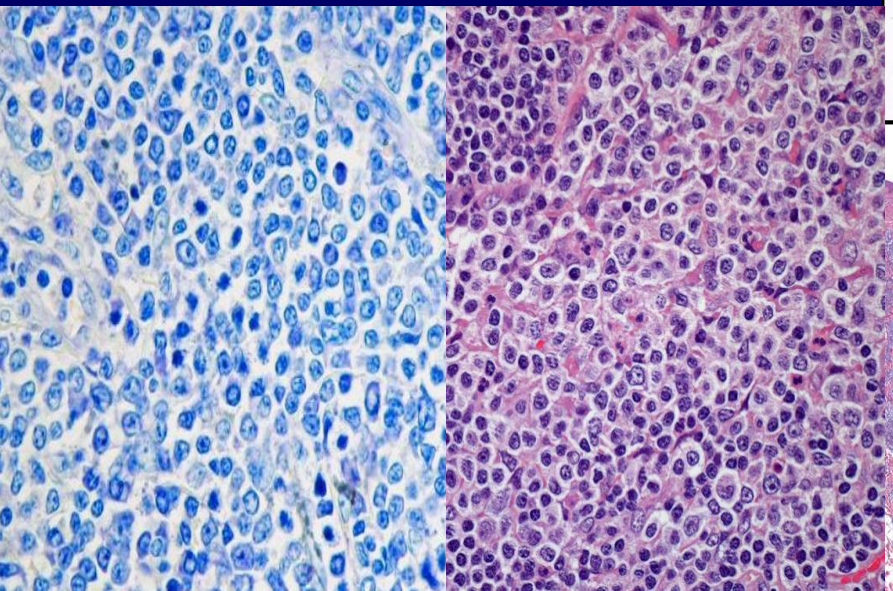
Fig. 5821 Primary cutaneous marginal zone lymphoma. Erythematous nodule on the upper back.

reported (1096,2544,2720). In a recent study, PCMZL was associated with high incidence rates of gastrointestinal disorders and autoimmune diseases (962).

Histopathology
PCMZL shows a dense dermal multinodular infiltrate of small lymphocytes, plasma cells, and follicles with reactive germinal centres (136,873,910,2544). The plasma cells are typically located at the periphery of the infiltrate and in the subepidermal compartment. In most cases, the small B cells have a lymphoplasmacytoid morphology. A predominance of monocytoid B cells and the expression of IgM should raise suspicion for a secondary cutaneous MALT lymphoma (664). Transformation to large B-cell lymphoma is very rare (1632).
The neoplastic B cells express B-cell markers including CD19, CD20, and CD79a. They are also BCL2-positive, but negative for CD5, CD10, BCL6, and cyclin D1 (see Table 75-5). The reactive germinal centres contain BCL6+ and BCL2– cells and are supported by networks of CD21+ follicular dendritic cells. The plasma cells show monotypic expression of immunoglobulin light chains in most cases. Reactive T cells



- Inizialmente espansione marginale con residue strutture follicolari, in seguito colonizzazione dei centri chiari
- In fase avanzata crescita anche diffusa, infiltrativa;
- modulazione secernente piu’ evidente alla periferia lesionale



In caso di regressione spontanea talora anetoderma (elastolisi immuno-mediata) ; associate patologie autoimmuni, disordini gastrointestinali e/o infezione HBV

MZL “ lipoma like ”: noduli sottocutanei (2-5 cm); tronco,arti; 54-75 anni; F>M; infez. HCV (genotipo 2a, 2b); crioglobulin. tipo II Prognosi >90% 5 anni; raro spread; possibile regressione spontanea Terapia antivirale

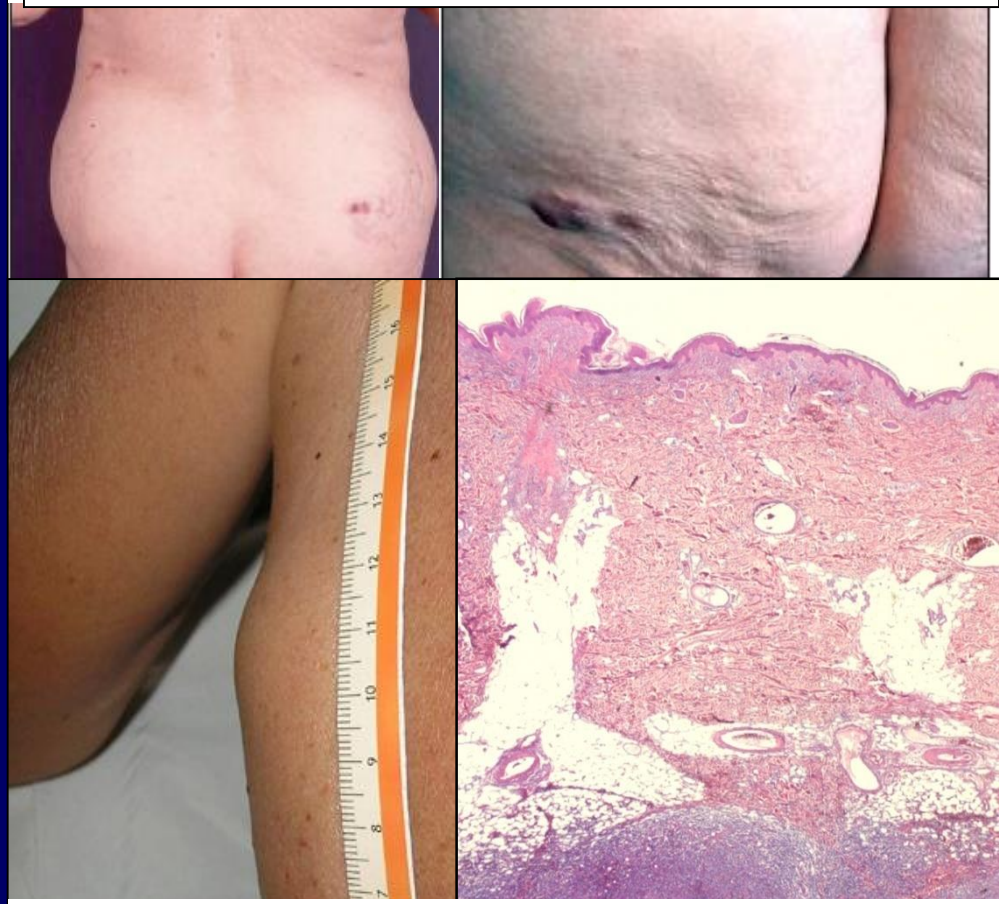
OBSERVATION

Anetodermic Primary Cutaneous B-Cell Lymphoma

A Unique Clinicopathological Presentation of Lymphoma Possibly Associated With Antiphospholipid Antibodies

Emmilia Hodak, MD; Hana Feuerman, MD; Aviv Barzilai, MD; Michael David, MD; Lorenzo Cerroni, MD; Meora Feinmesser, MD

•**Zattra E et al Clin Exp Dermatol 2009:34:e945**

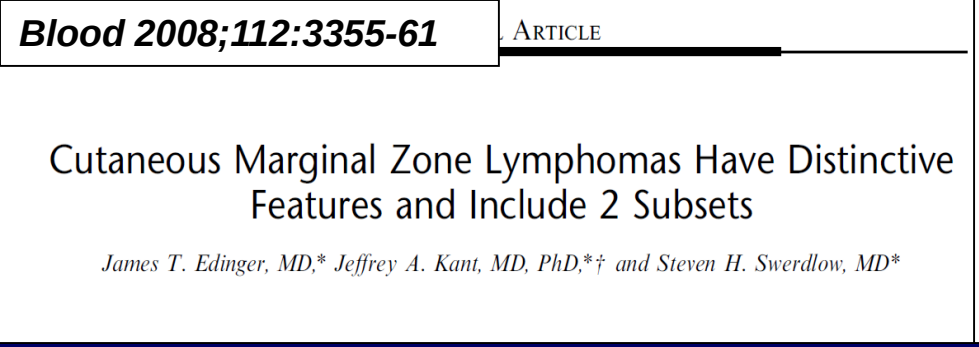


Subcutaneous ‘lipoma-like’ B-cell lymphoma associated with HCV infection: a new presentation of primary extranodal marginal zone B-cell lymphoma of MALT

M. Paulli[1]*, L. Arcaini[2], M. Lucioni[1], E. Boveri[1], D. Capello[3], F. Passamonti[2], M. Merli[2], S. Rattotti[2], D. Rossi[3], R. Riboni[1], E. Berti[1]

[1]Pathology Section, Department of Human Pathology; [2]Division of Her

Ann Oncol 2010;21:1189-1195



Blood 2008;112:3355-61

ARTICLE

Cutaneous Marginal Zone Lymphomas Have Distinctive Features and Include 2 Subsets

James T. Edinger, MD,* Jeffrey A. Kant, MD, PhD,*† and Steven H. Swerdlow, MD*

The majority of cutaneous marginal zone B-cell lymphomas expresses class-switched immunoglobulins and develops in a T-helper type 2 inflammatory environment

Febe van Maldegem,[1] Remco van Dijk,[1] Thera A. M. Wormhoudt,[1] Philip M. Kluin,[2] Rein Willemze,[3] Lorenzo Cerroni,[4] Carel J. M. van Noesel,[1] and R

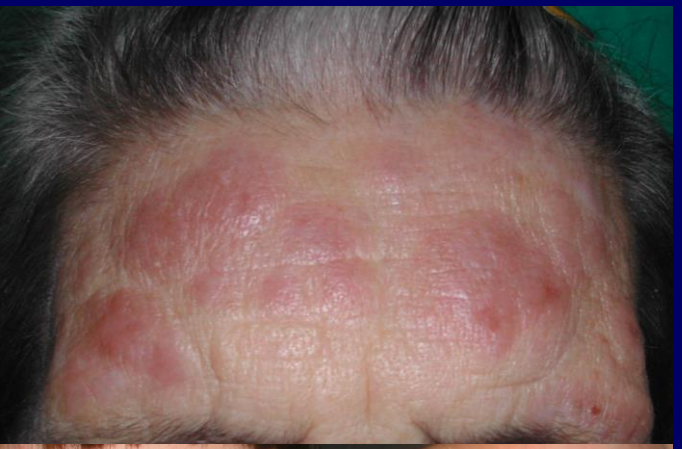
Am J Surg Pathol 2010;34:1830-41

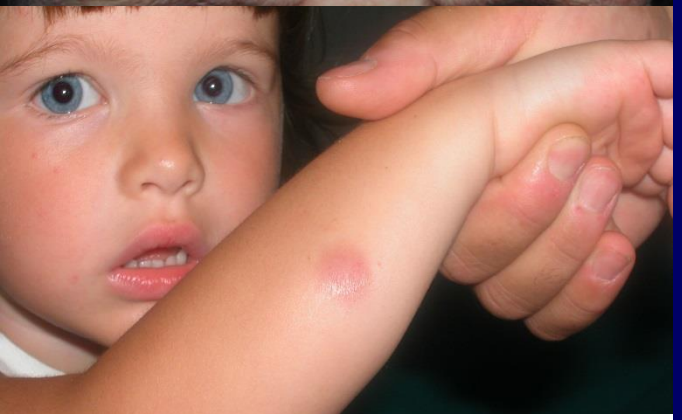
1-Heavy-chain class-switched form (IgG, IgA, o IgE) ; T reattivi; CXCR3-:disordini linfoproliferativi clonali cronici

2- Non-class switched form ,meno comune, (IgM+,CXCR3+) ; talora aggregati di grandi cellule

	PCMZL "switched" (IgG+)	PCMZL "non switched" (IgM+)
Pattern	Diffuse	Perivascular
Plasma-cells	+++	+
Monocytoid features	No	Present
Reactive T-cells	+++	+
CXCR3	Negative	Positive
Th2 background	Present	No
Mast cells	Present	No
Extracutaneous spread	No	Sometimes

LZM cutaneo *vs* pseudolinfoma

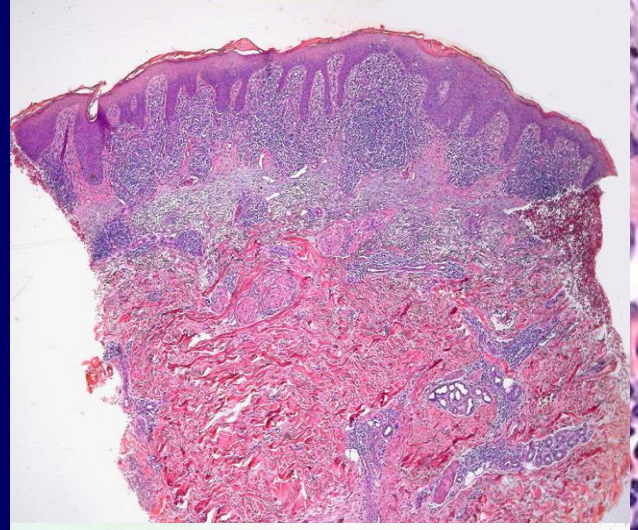


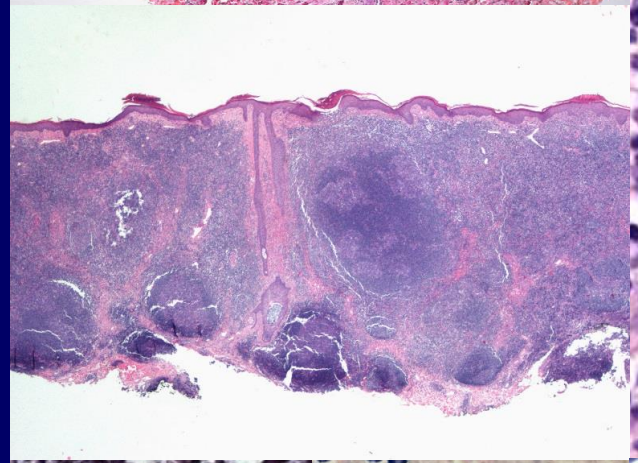


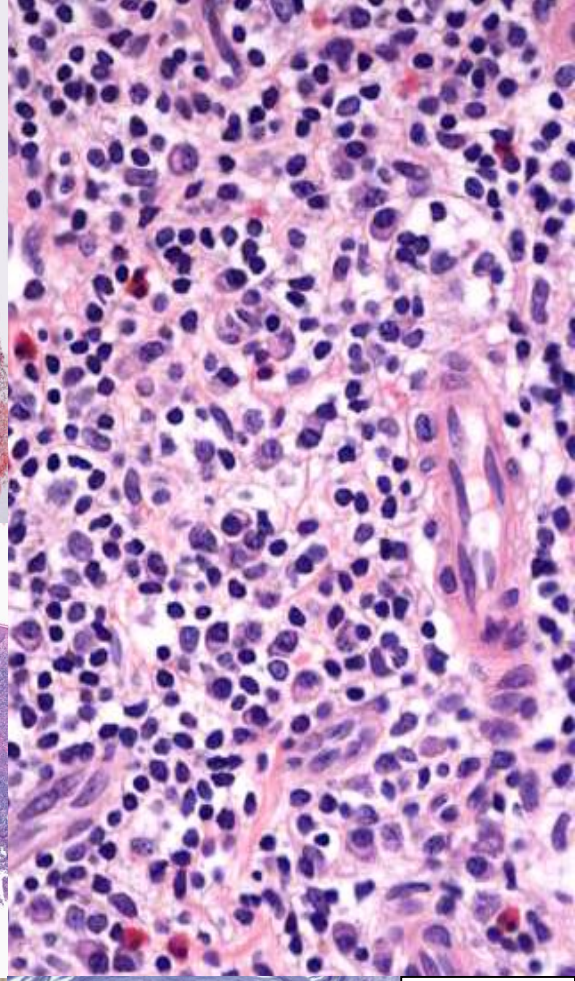
Demonstration of Clonal Immunoglobulin Gene Rearrangements in Cutaneous B-Cell Lymphomas and Pseudo-B-Cell Lymphomas: Differential Diagnostic and Pathogenetic Aspects

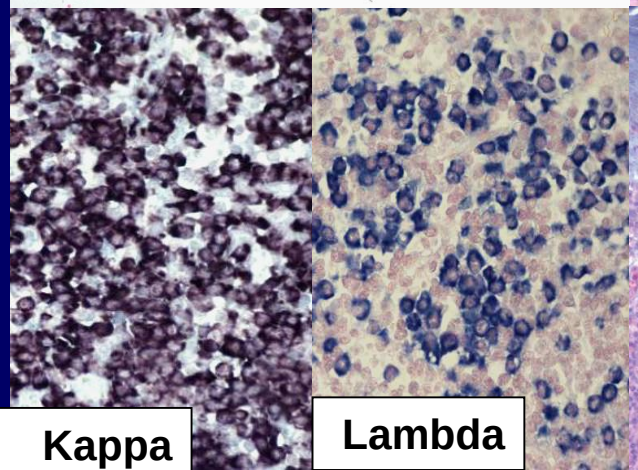
Udo Rijlaarsdam, Victor Bakels, Johan W. van Oostveen, Roel J.L. Gordijn, Marie-Louise Geerts, Chris J.L.M. Meijer, Rein Willemze

Departments of Dermatology (UR, VB, JWvO, RJLG, RW) and Pathology, Section of Molecular Pathology (JWvO, RJLG, CJLMM), Free University Hospital, Amsterdam, The Netherlands; and Department of Dermatology (M-LG), University Hospital, Gent, Belgium



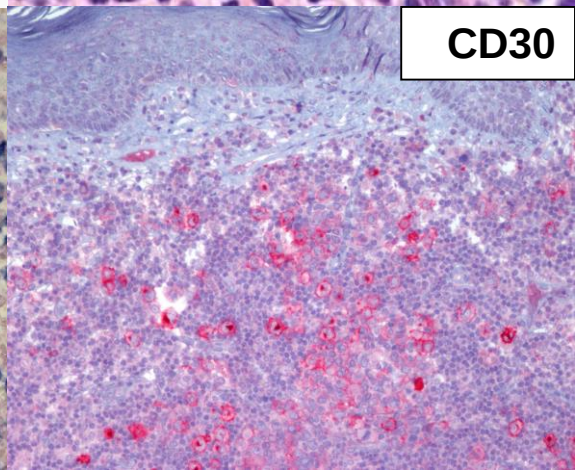






Kappa

Lambda



CD30

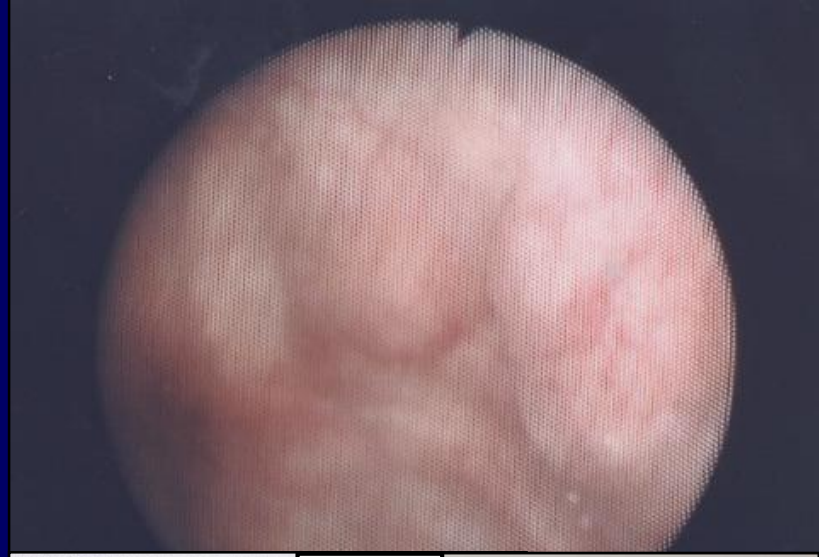
PZ F, 72 anni ; da 10 anni, cistiti recidivanti (E. Coli)

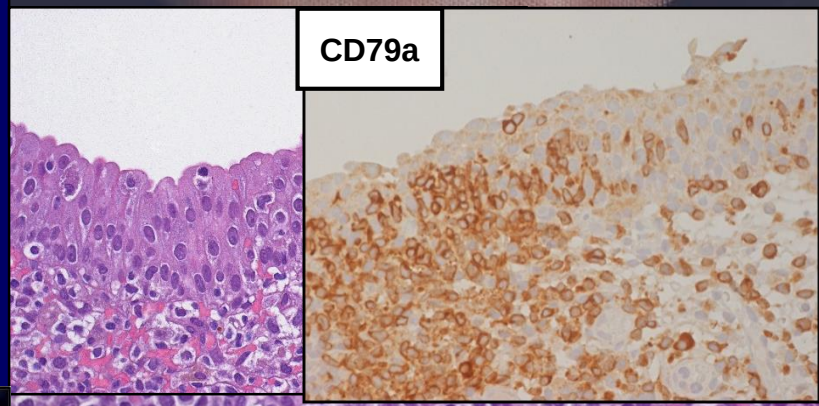
Cistoscopia: neoformazioni mammellonate (cm2,5); stadiazione negativa

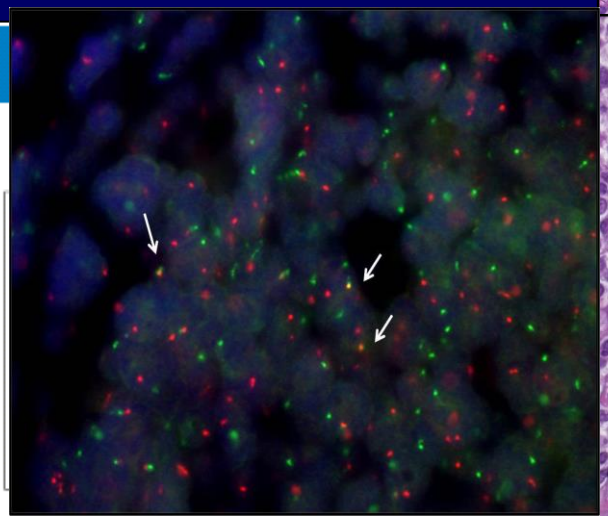
FISH t(11;18)(q21;q21) API2/MALT1 positiva

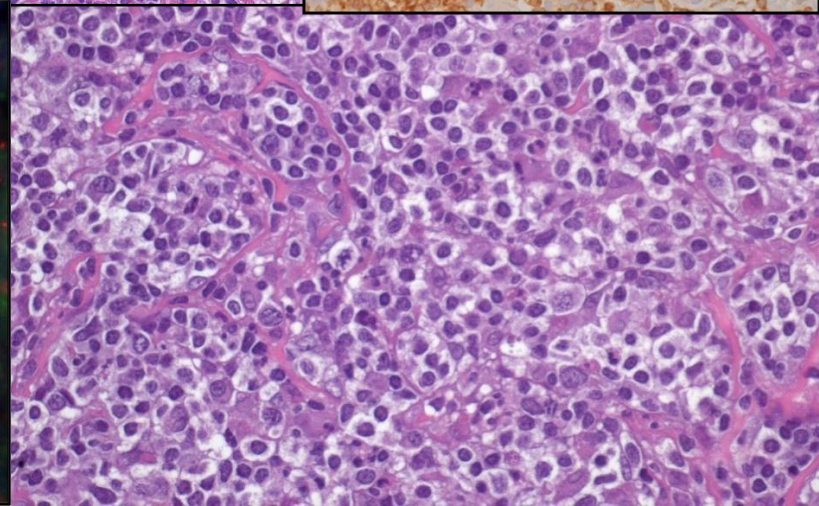
Terapia ciprofloxacina 6 settimane

Remissione completa a 18 mesi









JOURNAL OF CLINICAL ONCOLOGY

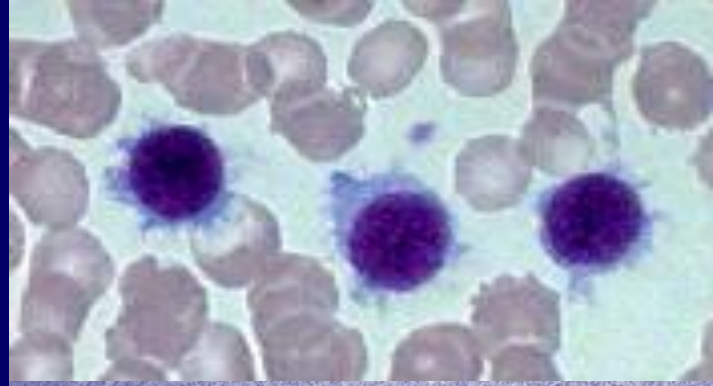
Antibiotic Therapy–Induced Remission of Bladder Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma Carrying t(11;18)(q21;q21) Apoptosis Inhibitor 2–*MALT1*

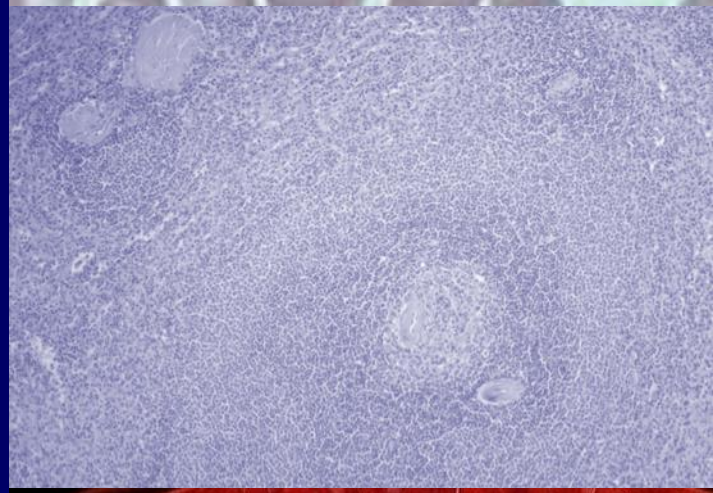
Introduction

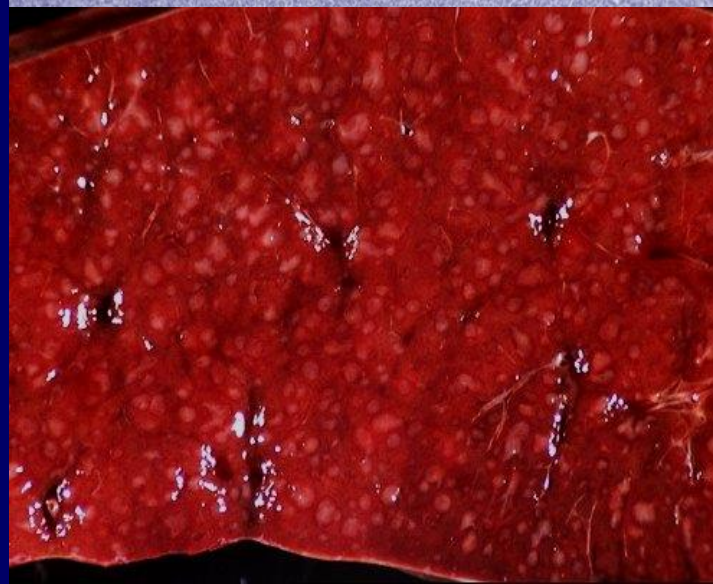
Primary urinary bladder involvement by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is exceedingly rare and accounts for less than 0.2% of all non-Hodgkin lymphomas (NHLs).[1,2] Because of its rarity, limited clinicopathologic data are available and result from single case observations or small series. This lymphoma is often associated with both recurrent infections and/or interstitial cystitis.[3-6] Clinically, urinary symptoms such as hematuria, dysuria, and urgency are the most

LZM Splenico

- M>F, VI-VII decade
- Milza e linfonodi ilo splenico, midollo e spesso sangue periferico; possibile coinvolgimento epatico
- Clinica: splenomegalia (>400 gr), anemia e trombocitopenia autoimmune ± linfociti villosi nel sangue periferico; 1/3 dei casi ha componente monoclonale
- Associazione infezione da HCV







Brief report

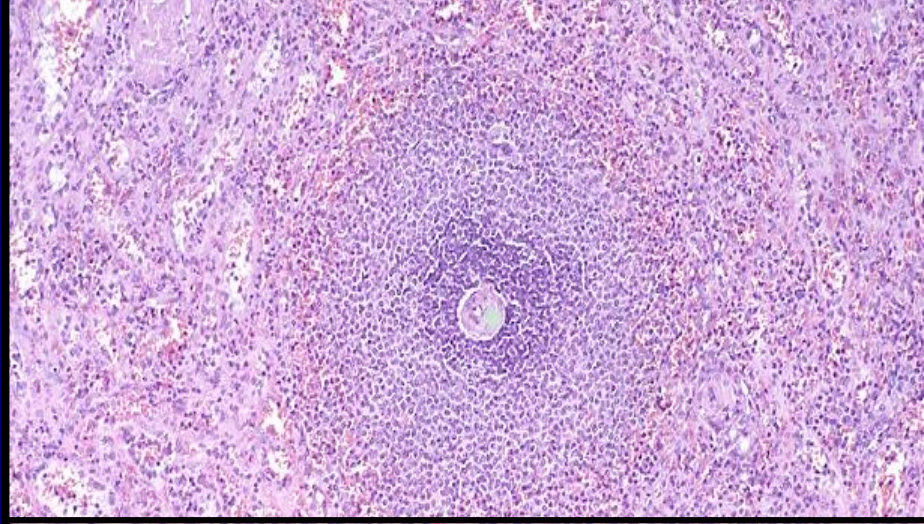
Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?

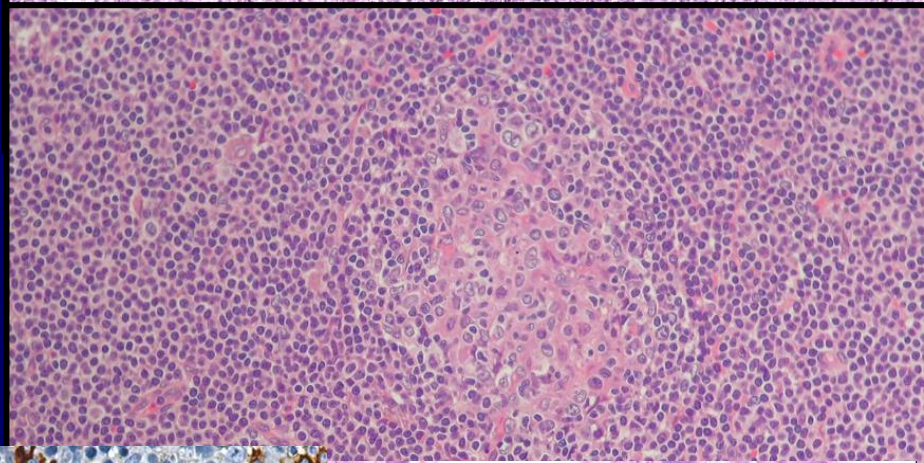
David Saadoun, Felipe Suarez, François Lefrere, Françoise Valensi, Xavier Mariette, Achille Aouba, Caroline Besson, Bruno Xavier Troussard, Patrice Cacoub, and Oliver Hermine

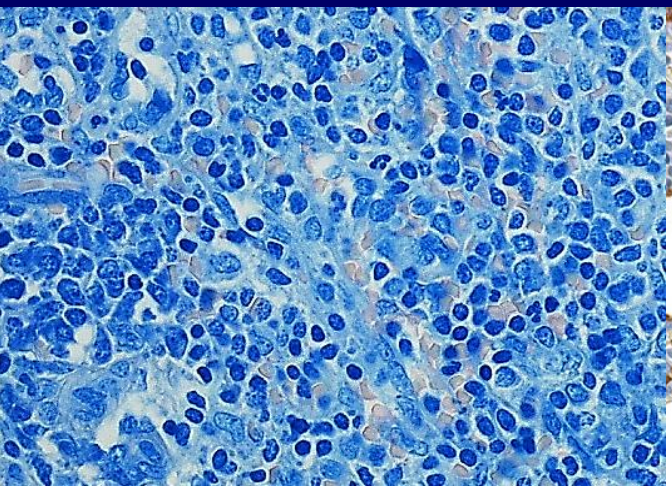
Hepatitis C virus (HCV) has been associ- was symptomatic in 13 (72%). All patients response, monoclonal im ated with the development of B-cell no Hodgkin lymphomas. We recently report the regression of splenic lymphoma wi

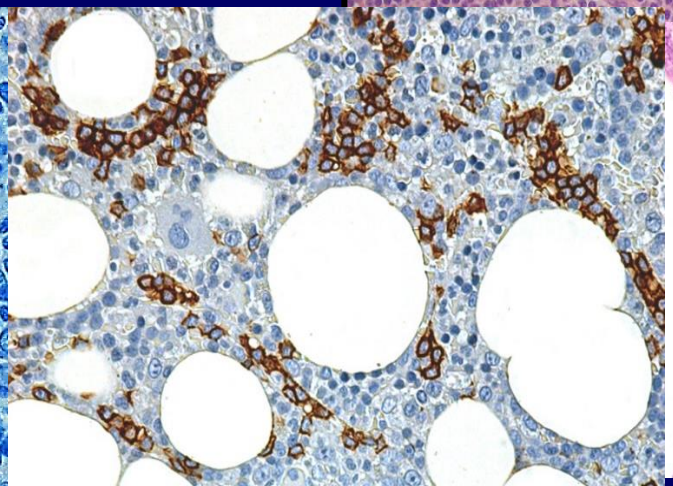
Saadoun et al. Blood 2005;105: 74

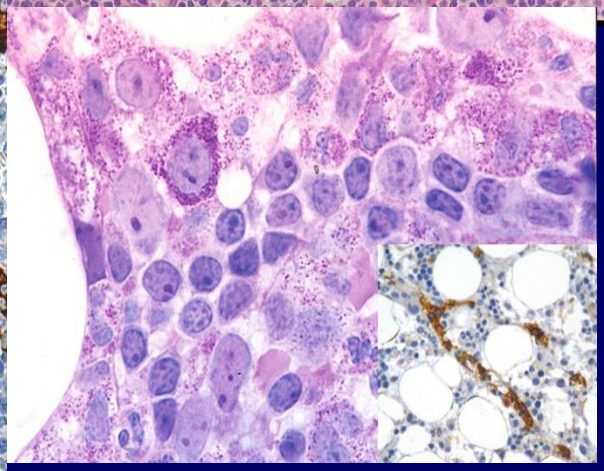
- Noduli polpa bianca
- Cellule monocitoidi ad anello intorno ai follicoli della polpa bianca, cellule centrocito-simili che colonizzano i centri chiari germinativi
- Spesso infiltrazione polpa rossa
- Istiociti epitelioidi
- Infiltrazione sinusale midollare



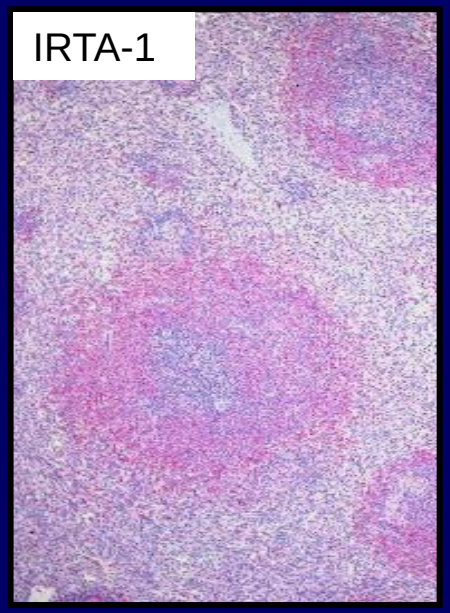


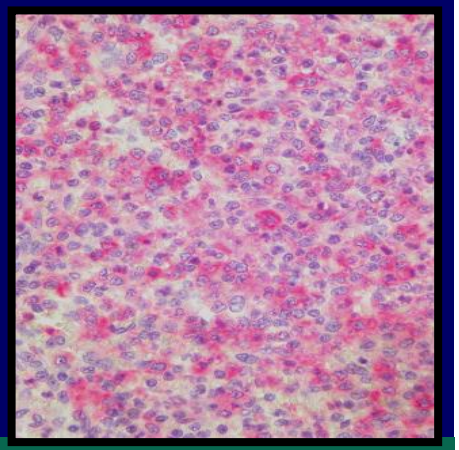


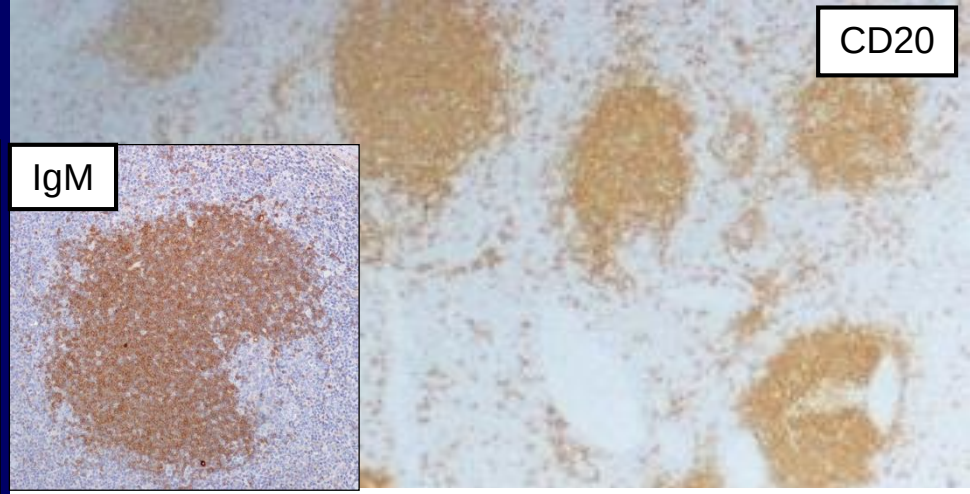




- CD20+
- CD10-
- CD79a+
- CD11c+/-
- IgM+
- CD5-/+
- CD43+/-
- Bcl-1-
- Bcl-2+
- CD23-
- IRTA-1+/-







	SMZL	LPL	SDRPL	HCL-v	HCL	EMZL/ NMZL	CLL	MCL	FL
CD20	+	+	+	+	+	+	−/+	+	+
CD79a	+	+	+	+	+	+	+	+	+
CD5	−/+	−/+	−/+	−	−	−/+	+	+	−
CD21	−/+	−	−	−	−	−	−	−	−
CD23	−/+	−/+	−	−	−	−/+	+	−	−/+
BCL1	−	−	−	−/+	+	−	−	+	−
DBA44	+/−	−	+	+	+	−	−/+	−	−
Annexin A1	−	−	−	−	+	−	−	−	−
CD103	−	−	−	+/−	+	−	−	−	−
CD123	−	−	−	−	+	−	−	−	−
IRTA1	−	−	−	−	−	+/−	−	−	−
IgM	+	+	+	+	+	+	+	+	+
IgD	+/−	−	−/+	+	+	−/+	+	+	+
CD10	−	−*	−	−	−	−	−	−*	+/−
BCL6	−	−	−	−	−	−/+	−	−/+	+
CD43	−/+	−	−	−	−	−/+	+	+	−
SOX11	−	−	−	−	−	−	−	+	−
LEF1	−	−	−	−	−	−	+	−/+	−

−, <25% of cases; −/+, 25%-50% of cases; +/−, 50%-75% of cases; +, >75% of cases.

FL, follicular lymphoma; NMZL, nodal marginal zone lymphoma; SDRPL, splenic diffuse red pulp lymphoma.

*Sporadic cases reported.

Review Series

INDOLENT B-CELL LYMPHOMA

Splenic marginal zone lymphoma: from genetics to management

Luca Arcaini,[1,2] Davide Rossi,[3] and Marco Paulli[1,4]

LZM MALT, anomalie citogenetiche e sede

	t(11;18) (q21;q21)	t(14;18) (q32;q21)	t(3;14) (p14;q32)	t(1;14) (p22;q32)	+3	+8
Stomaco	6-26%	1-5%	0	0	11%	6%
Intestino	12-56%	0	0	0-13%	75%	25%
Annessi oculari	0-10%	0-25%	0-20%	0	38%	13%
Ghiandole salivari	0-5%	0-16%	0	0-2%	55%	19%
Polmone	31-53%	6-10%	0	2-7%	20%	7%
Tiroide	0-17%	0	0-50%	0	17%	0
Cute	0-8%	0-14%	0-10%	0	20%	4%

Am J Surg Pathol 2006;30:1546-53

The Incidence and Anatomic Site Specificity of Chromosomal Translocations in Primary Extranodal Marginal Zone B-cell Lymphoma of Mucosa-associated Lymphoid Tissue (MALT Lymphoma) in North America

Ellen D. Remstein, MD, Ahmet Dogan, MD, Richard R. Einerson, BSMT (ASCP), Sarah F. Paternoster, BS, Stephanie R. Fink, BA, Mark Law, BS, Gordon W. Dewald, PhD, and Paul J. Kurtin, MD

Leukemia (2004) 18, 1722–1726

www.nature.com/leu

Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites

B Streubel[1], I Simonitsch-Klupp[1], L Müllauer[1], A Lamprecht[1], D Huber[1], R Siebert[2], M Stolte[3], F Trautinger[4], J Lukas[5], A Püspök[6], M Formanek[7], T Assanasen[8], H-K Müller-Hermelink[8], L Cerroni[9], M Raderer[10] and A Chott[1]

[1]Institute of Pathology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria; [2]Institute of Human Genetics, University Hospital Schleswig-Holstein, Campus Kiel, Germany; [3]Department of Pathology, Klinikum Bayreuth, Bayreuth, Germany; [4]Institute of Dermatology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria; [5]Institute of Ophthalmology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria; [6]Division of Gastroenterology, Internal Medicine IV, Vienna General Hospital, Medical University of Vienna, Vienna, Austria; [7]Division of Oto-Rhino-Laryngology,

Leukemia 2004;18:1722-26

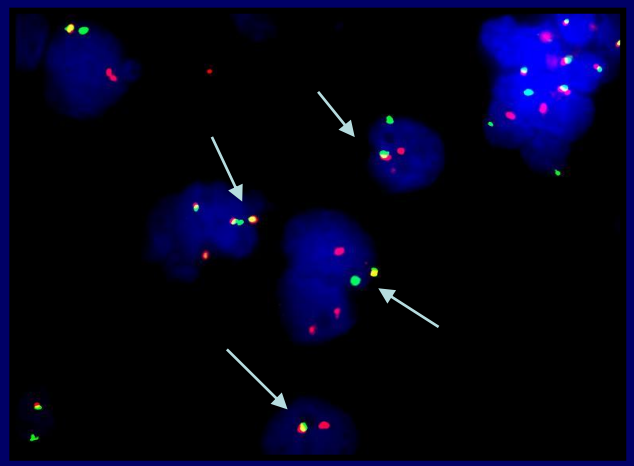
Linfomi MALT: anomalie citogenetiche

Tre traslocazioni convergono sullo stesso “signaling”

t(1;14)	t(11;18)	t(14;18)
Deregolazione *BCL10*	Fusione *API2/MALT1*	Deregolazione *MALT1*
Rara	Frequente	MALT-omi non gastroent

Attivazione NF-kB

Fattore di trascrizione, attiva proliferazione cellulare



Linfomi MALT antibiotico resistenti

- t(3;14)(p14.1;q32) geni *IGH* e *FOXP1*
- Trisomia 3, trisomia 18

Genetica

NOTCH pathway (SMZL)
(*NOTCH1, NOTCH2, SPEN KLF2, KLF4*)

NF-kB pathway (NMZL)
(*MYD88, BIRC3, IKBKB, TNFAIP3, TRAF3*)

Mutazioni TP53

Alterazioni citogenetiche:
del 7q (30%), gain 3 e 18

Prognosi

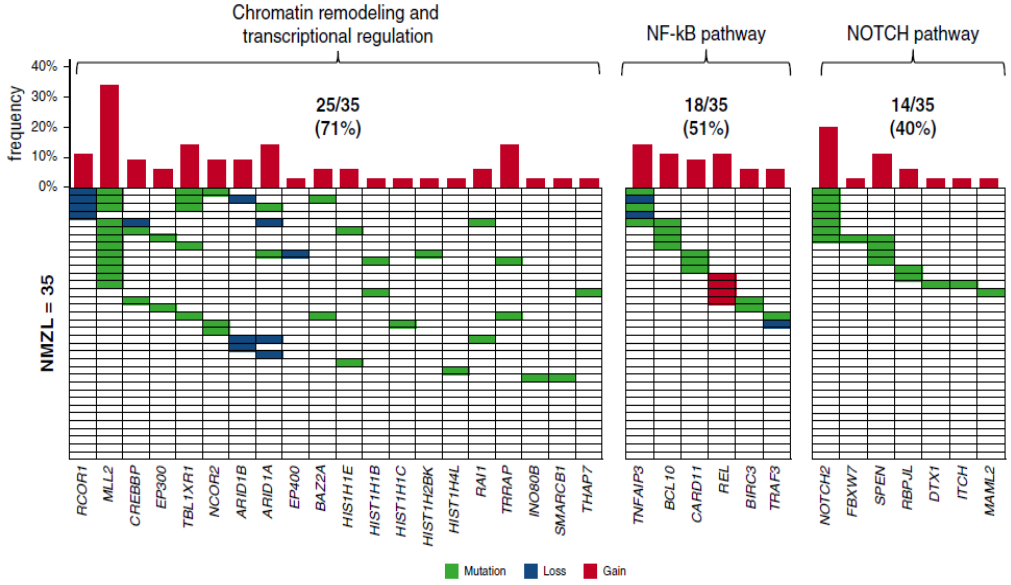
OS 10 anni 67-95%;
mutazioni NOTCH2, KLF2 e TP53 hanno significato prognostico sfavorevole

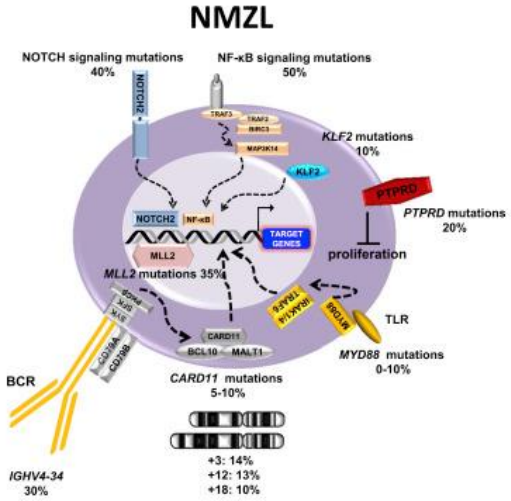
Regular Article blood

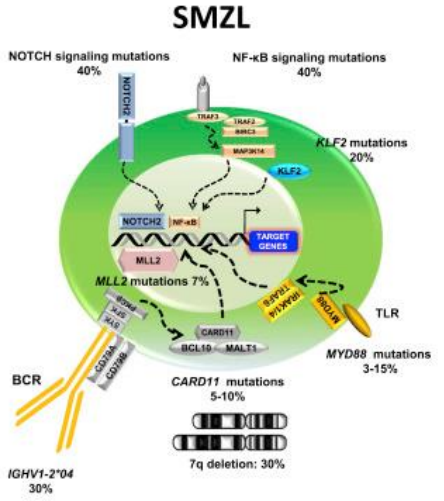
LYMPHOID NEOPLASIA

The genetics of nodal marginal zone lymphoma

Valeria Spina,[1,*] Hossein Khiabanian,[2,*] Monica Messina,[3] Sara Monti,[1] Luciano Cascione,[4] Alessio Bruscaggin,[1] Elisa Spaccarotella,[1] Antony B. Holmes,[5] Luca Arcaini,[6] Marco Lucioni,[7] Fabrizio Tabbò,[8] Sakellarios Zairis,[2] Fary Diop,[1] Michaela Cerri,[1] Sabina Chiaretti,[3] Roberto Marasca,[9] Maurilio Ponzoni,[10] Silvia Deaglio,[11] Antonio Ramponi,[12] Enrico Tiacci,[13] Laura Pasqualucci,[5] Marco Paulli,[7] Brunangelo Falini,[13] Giorgio Inghirami,[8,14,15] Francesco Bertoni,[4] Robin Foà,[3] Raul Rabadan,[2] Gianluca Gaidano,[1] and Davide Rossi[1,4]

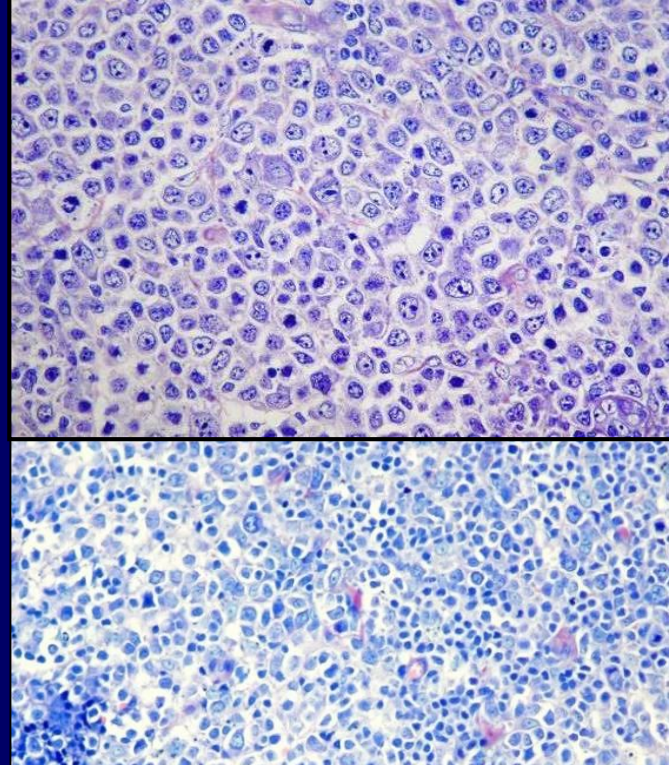






MZL: trasformazione in alto grado

- 50% MZL ha componente di grandi cellule
- Rischio trasformazione 5 % a 10 anni spesso DLBCL (nGC)
- Anomalie citogenetiche MZL rimangono nella componente trasformata
- 1/3 pz trasformati muoiono a 12 mesi < risposta terapia; < PFS ma uguale OS rispetto a de novo DLBCL



Best Practice & Research Clinical Haematology 30 (2017) 131–138

Transformation of marginal zone lymphoma (and association with other lymphomas)

Carla Casulo*, Jonathan Friedberg

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Histologic transformation in marginal zone lymphomas†

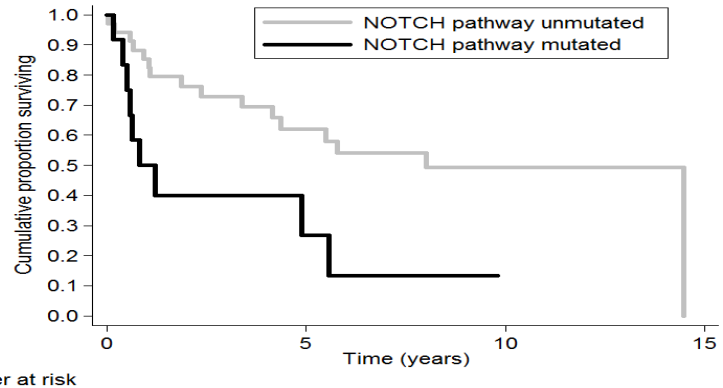
A. Conconi[1,2,‡*], S. Franceschetti[1,‡], K. Aprile von Hohenstaufen[3], G. Margiotta-Casaluci[1], A. Stathis[3], A. A. Moccia[3], F. Bertoni[3,4], A. Ramponi[5], L. Mazzucchelli[6], F. Cavalli[3], G. Gaidano[1] & E. Zucca[3]

Articles

Non-Hodgkin Lymphoma

The NOTCH pathway is recurrently mutated in diffuse large B-cell lymphoma associated with hepatitis C virus infection

Luca Arcaini,[1,2] Davide Rossi,[3] Marco Lucioni,[4] Marta Nicola,[1] Alessio Bruscaggin,[3] Valeria Fiaccadori,[1] Roberta Riboni,[4] Antonio Ramponi,[5] Virginia V. Ferretti,[2] Stefania Cresta,[3] Gloria Margiotta Casaluci,[3] Maurizio Bonfichi,[2] Manuel Gotti,[2] Michele Merli,[6] Aldo Maffi,[1] Mariarosa Arra,[1] Marzia Varettoni,[2] Sara Rattotti,[2] Lucia Morello,[1] Maria Luisa Guerrera,[1] Roberta Sciarra,[1] Gianluca Gaidano,[3*] Mario Cazzola,[1,2*] and Marco Paulli[1,4*]



Take home message

- MZL: eterogenei per presentazione clinica e biologia
- MZL: modello di linfomagenesi, nel quale interagiscono fattori ambientali (agenti infettivi) e fattori correlati alla risposta immune dell'ospite.
- MZL associati ad agenti infettivi : d.d. con quadri reattivi e implicazioni terapeutiche relativamente a strategie terapeutiche meno aggressive
- Alterazioni "pathways" NOTCH e NFkB, variabili per frequenza e tipologia nelle varie forme di MZL
- Progressione in alto grado: necessari criteri istopatologici più precisi anche in termini quantitativi

Ringraziamenti

- Dott. M.Lucioni
- Dr.ssa E.Boveri
- Dott. Arturo Bonometti
- Dott.ssa Sara Fraticelli
- Dott.ssa Roberta Riboni
- Prof. R. Bruno
- Dr.D.Rossi
- Prof. L.Arcaini

Genetica

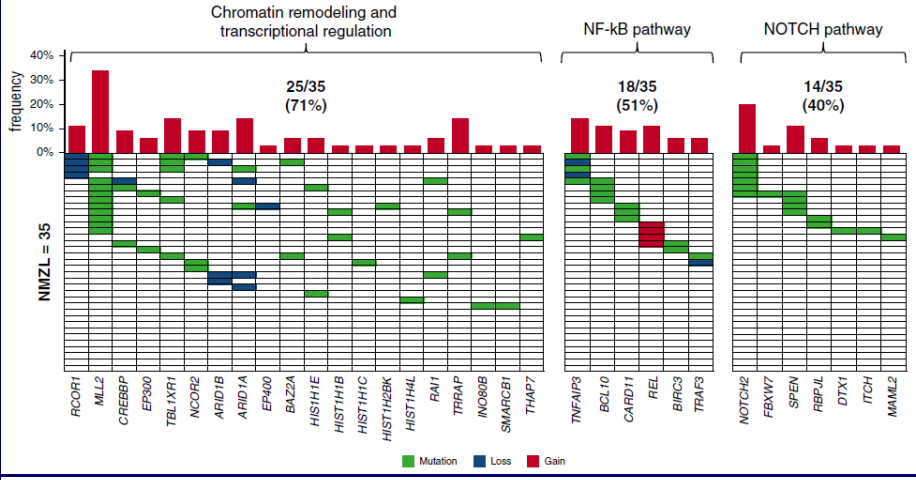
- Riarrangiamento clonale geni IG ; mutazioni spesso a carico IGHV3 e IGHV4 (IGHV1-69 forme HCV correlate)
- “Gains” cromosomi 3 e 18; perdita 6q23-24 come MALT e SMZL
- Non delezioni 7q31 e/o traslocazioni tipiche MALT
- Pattern mutazionale simile a SMZL (attivazione “pathways” NOTCH e NFKB)
- Mutazioni PTPRD 20%
- Prognosi: 60-70% a 5 anni

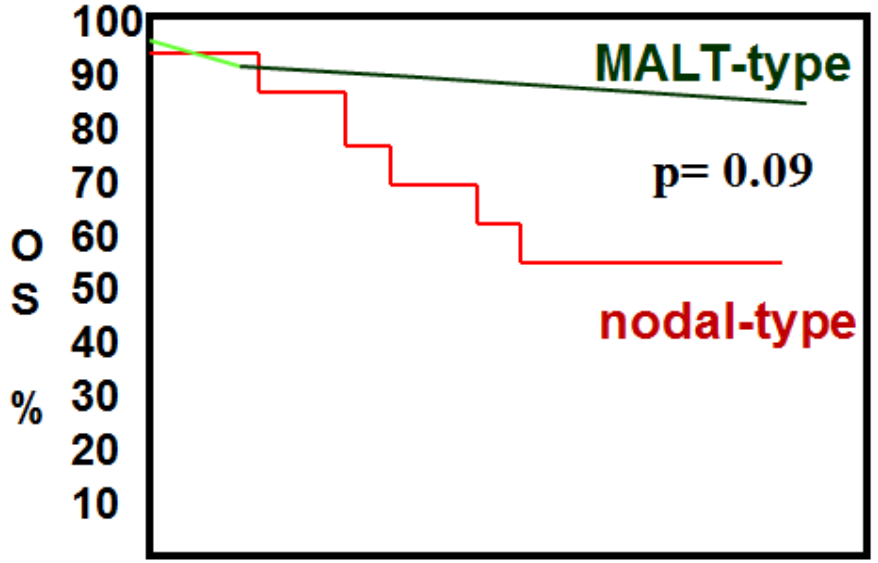
Regular Article blood

LYMPHOID NEOPLASIA

The genetics of nodal marginal zone lymphoma

Valeria Spina,[1,*] Hossein Khiabanian,[2,*] Monica Messina,[3] Sara Monti,[1] Luciano Cascione,[4] Alessio Bruscaggin,[1] Elisa Spaccarotella,[1] Antony B. Holmes,[5] Luca Arcaini,[6] Marco Lucioni,[7] Fabrizio Tabbò,[8] Sakellarios Zairis,[2] Fary Diop,[1] Michaela Cerri,[1] Sabina Chiaretti,[3] Roberto Marasca,[9] Maurilio Ponzoni,[10] Silvia Deaglio,[11] Antonio Ramponi,[12] Enrico Tiacci,[13] Laura Pasqualucci,[5] Marco Paulli,[7] Brunangelo Falini,[13] Giorgio Inghirami,[8,14,15] Francesco Bertoni,[4] Robin Foà,[3] Raul Rabadan,[2] Gianluca Gaidano,[1] and Davide Rossi[1,4]





Il microambiente del LZM cutaneo

- Spesso prominente
- Linfociti T CD3+ (CD4>CD8)
- Plasmacytoid dendritic cells CD123+, Tfh PD1+
- Scarsi Treg CD25+, Tcitotox TIA1+

	PCMZL "switched" (IgG+)	PCMZL "non switched" (IgM+)
Pattern	**Diffuso**	**Perivascolare**
Plasmacellule	**+++**	**+**
Componente B simil monocitoide	**Assente**	**Presente**
Infiltrato T-cellulare	**+++**	**+**
Mastociti	**Sì**	**No**
CXCR3	**-**	**+**
Th2 background	**Sì**	**No**
Disseminazione extracutanea	**No**	**Possibile**

The majority of cutaneous marginal zone B-cell lymphomas expresses class-switched immunoglobulins and develops in a T-helper type 2 inflammatory environment

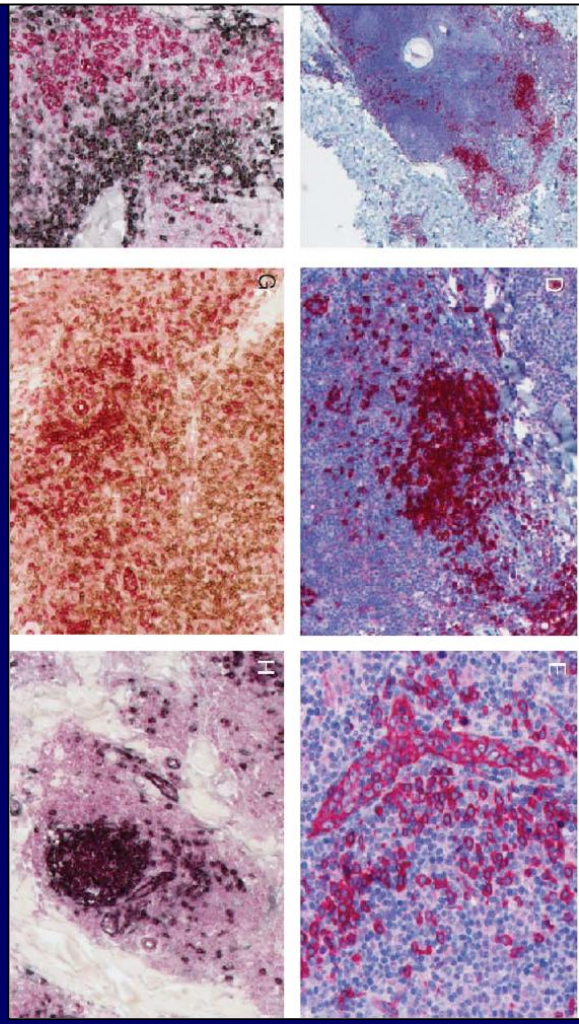
Febe van Maldegem,[1] Remco van Dijk,[1] Thera A. M. Wormhoudt,[1] Philip M. Kluin,[2] Rein Willemze,[3] Lorenzo Cerroni,[4] Carel J. M. van Noesel,[1] and Richard J. Bende[1]

ORIGINAL ARTICLE

Cutaneous Marginal Zone Lymphomas Have Distinctive Features and Include 2 Subsets

James T. Edinger, MD, Jeffrey A. Kant, MD, PhD,*† and Steven H. Swerdlow, MD**

Am J Surg Pathol 2010;34:1830-41



NOTCH pathway 40%

(*NOTCH1, NOTCH2, SPEN KLF2, KLF4*)

NF-kB pathway 25%

(*MYD88, BIRC3, IKBKB, TNFAIP3, TRAF3*)

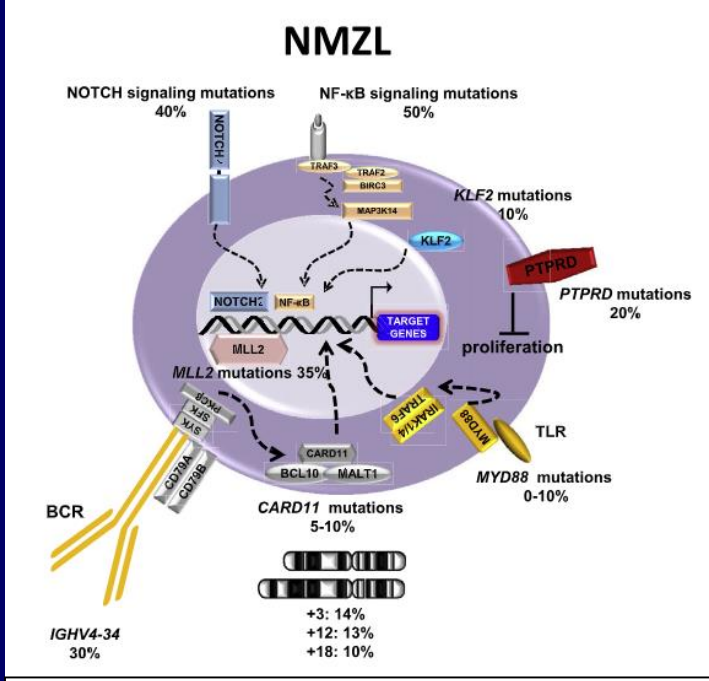
TP53

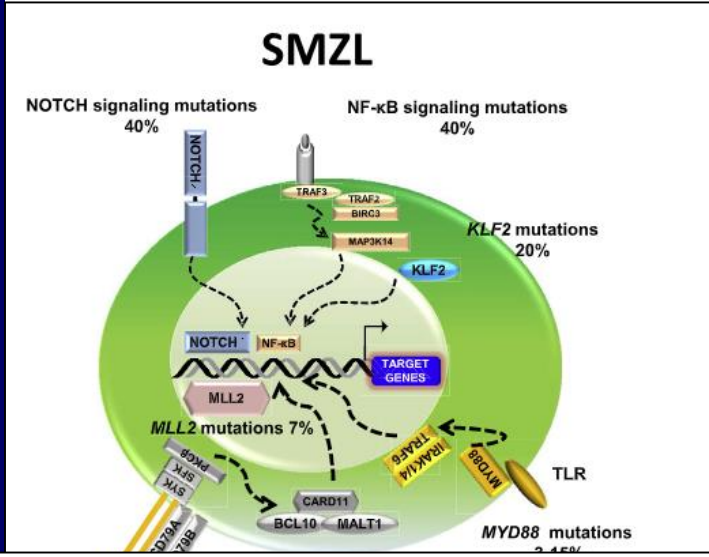
Alterazioni citogenetiche

- Delezione 7q (30%)
- Non t riscontrabili in altri linfomi B ad es. t(11;14), t(14;18), non t tipiche MALTomi

Prognosi

OS 67-95% 10 anni;mutazioni NOTCH2, KLF2 e TP53 significato prognostico sfavorevole





Best Practice & Research Clinical Haematology 30 (2017) 5–12

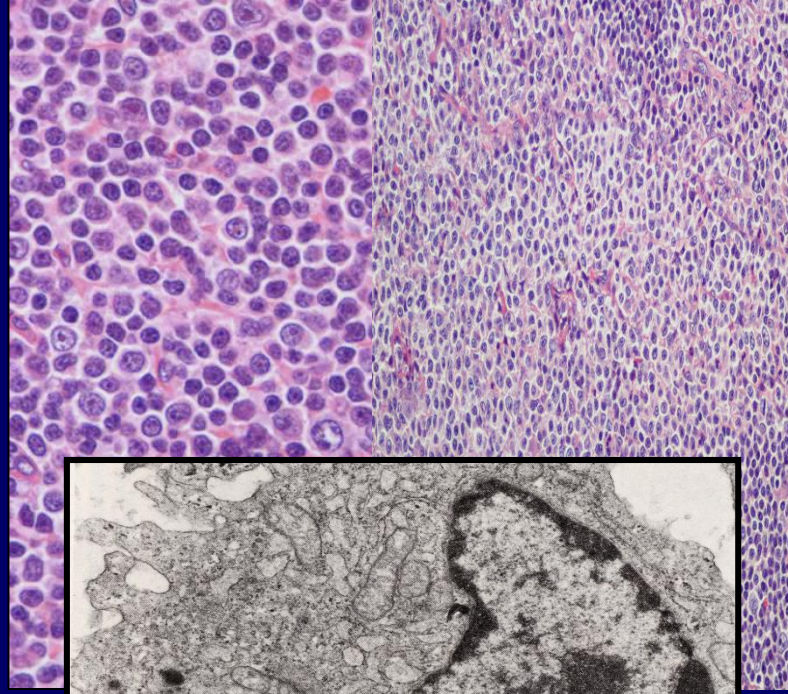
Molecular pathogenesis of splenic and nodal marginal zone lymphoma

Valeria Spina, Davide Rossi*

Hematology, Institute of Oncology Research and Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

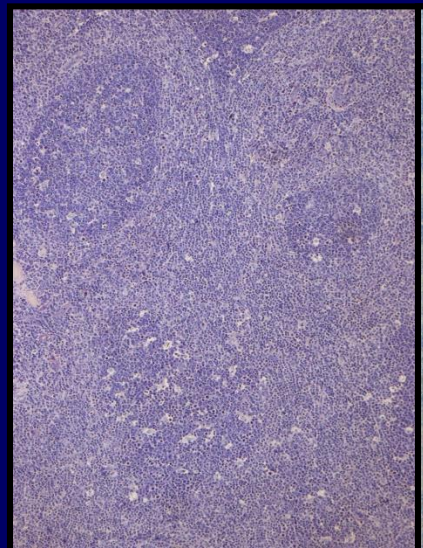
Citologia

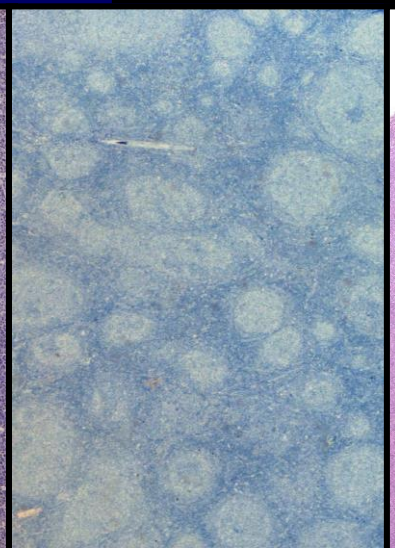
- Piccole cellule; citoplasma scarso; nuclei centrocito simili, tondi vs modicamente irregolari; alla periferia ZM le cellule hanno citoplasma piu' ampio, nuclei vagamente reniformi, simil-monocitoidi
- Ultrastruttura: piccoli mitocondri, cisterne reticolo endoplasmatico rugoso, Golgi ben sviluppato

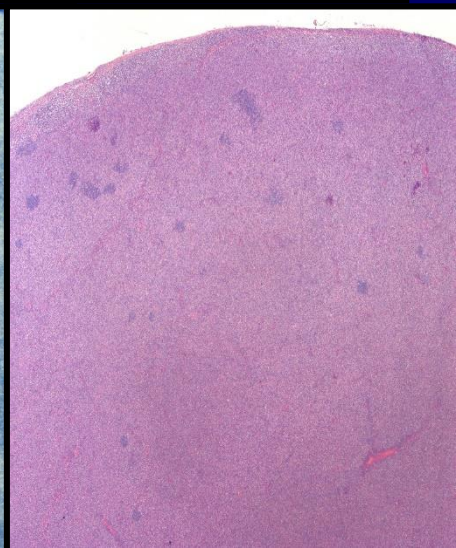


"Patterns"

- Sinusale/Marginale
- Nodulare
- Diffuso

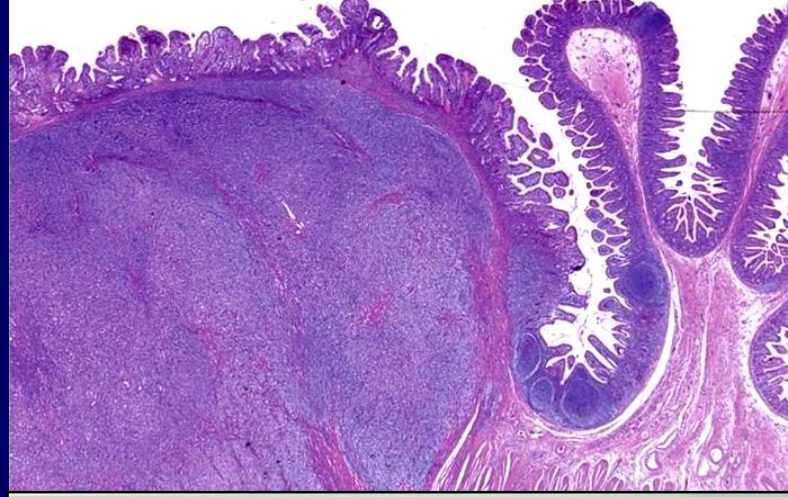


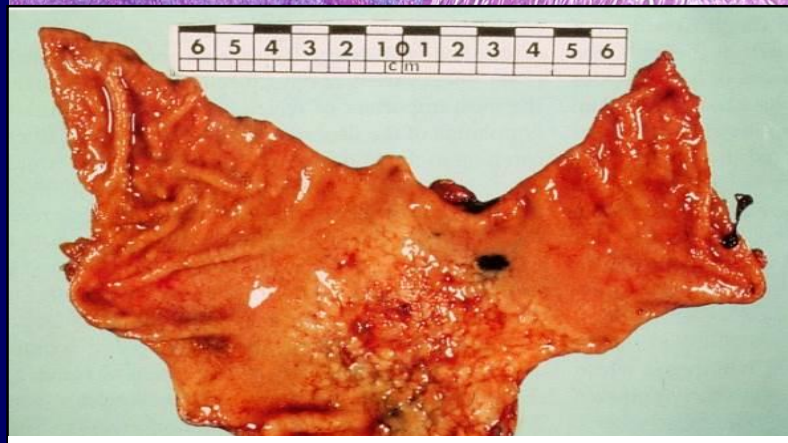


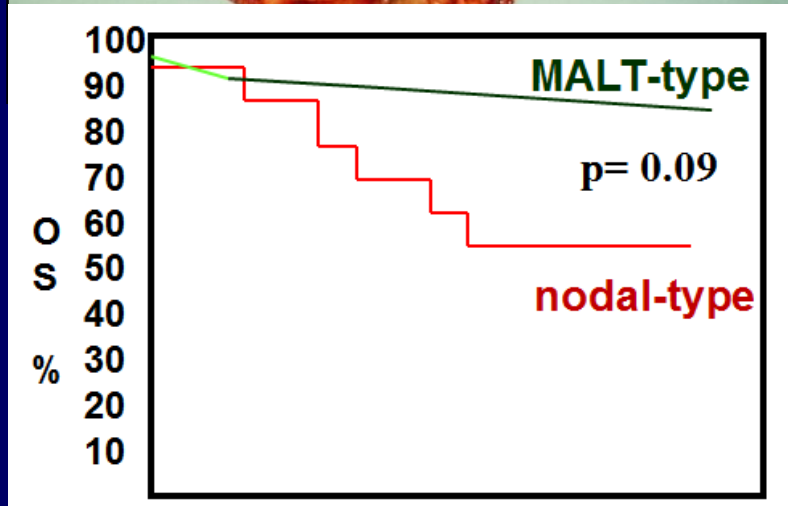


LZM extranodale MALT-type (7-8% LNH)

- M=F, nelle donne più frequentemente a carico della tiroide e delle ghiandole salivari, VII decade
- Elevata incidenza nel Nord-Est dell'Italia (?)
- Associazione eziologica con infiammazione cronica: infezioni (Helicobactyer pylori, Borrelia burgdoferi), malattie autoimmuni (Sjogren, Hashimoto)
- Sedi più colpite : stomaco (35%), occhi ed annessi oculari (13%), cute (9%), polmoni (9%), ghiandole salivari (8%), tiroide (2%)
- Stadio all'esordio: I/II, 30-40% coinvolgimento di sedi extranodali multiple

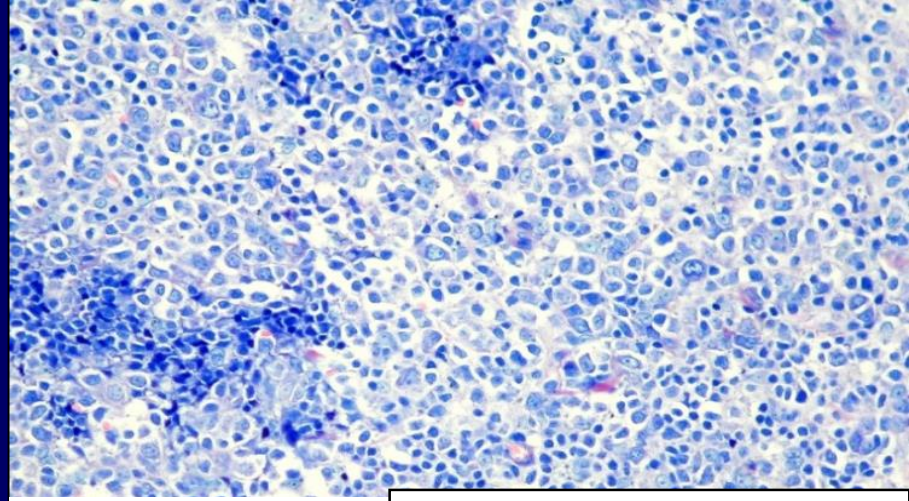






MZL e HCV+ DLBCL

- 1/3 DLBLCL HCV+ ha una componente a medie cellule simil-monocitoidi
- Mutazioni “pathways” NOTCH nel 25% HCV+ DLBCL
- Trasl. MLT1 nel14% HCV+ DLBCL
- Età, traslocazione MALT1, mutazioni pathway NOTCH peggiorano sopravvivenza
- Verisimile quota HCV+ DLBCL rappresentino trasfomazione di un clone clinicamente non identifica



Haemathol. 2015; 100:246-252

Articles

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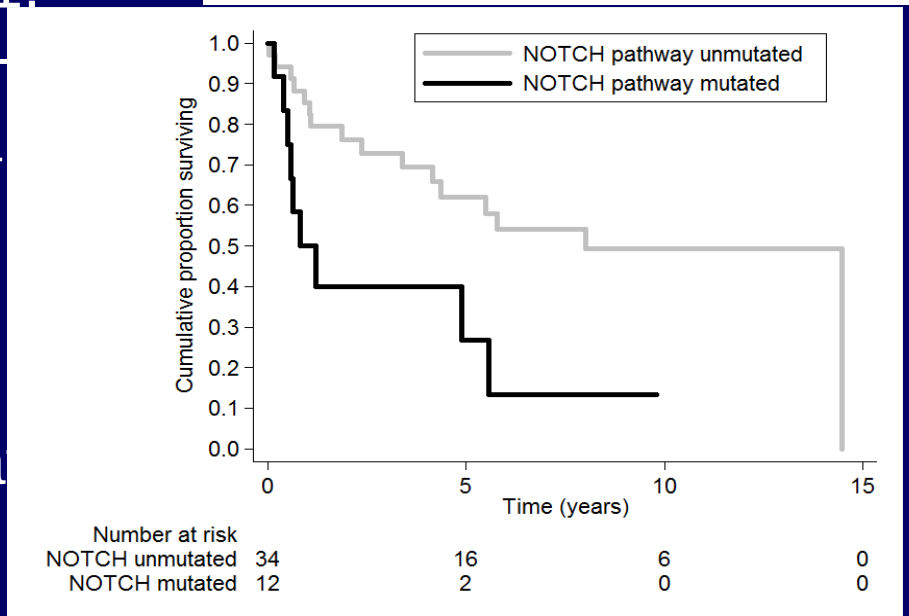
[1]Department of Molecular Medicine, University of Pavia; [2]Department of Hematology Oncology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia; [3]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara; [4]Department of Pathology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia; [5]Division of Pathology, Department of Health Science, Amedeo Avogadro University of Eastern Piedmont, Novara; and [6]Division of Hematology, Ospedale di Circolo e Fondazione Macchi, University of Insubria, Varese, Italy



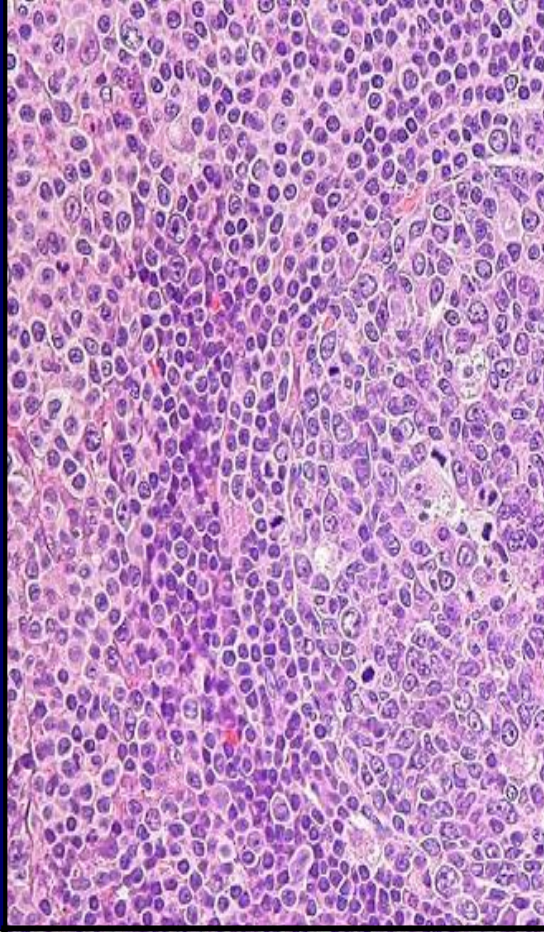
La storia

1959 Lennert: sinusoidal histiocytes

1961 Stansfeld: monocytoid cells

1984 De Almeda: large sinus lymphocytes

1984 Sheibani: monocytoid B



Monocytoid B-Cell Lymphoma

A Novel B-Cell Neoplasm

KHALIL SHEIBANI, MD, CARL C. SOHN, MD, JEROME S. BURKE, MD, CARL D. WINBERG, MD, ANNA M. WU, PhD, and HENRY RAPPAPORT, MD

From the James Irvine Center for the Study of Leukemia and Lymphoma, Division of Anatomic Pathology, City of Hope National Medical Center, Duarte, California

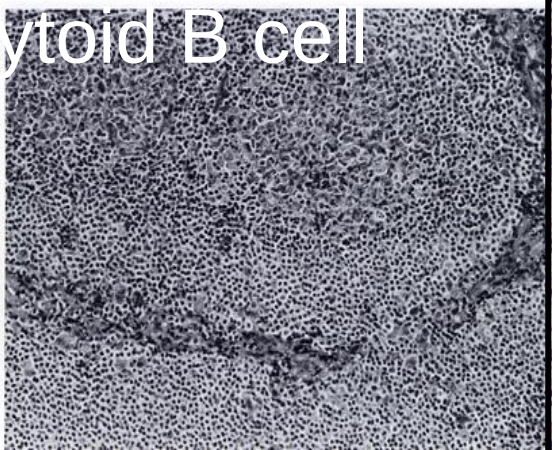
Monocytoid B lymphocytes (MBLs), originally described as part of the histologic picture of toxoplasmic lymphadenitis, have been recognized as a reactive component in a variety of lymph node disorders. The authors now report 3 cases of non-Hodgkin's lymphoma in which a multidisciplinary approach allowed them to confirm the ex-

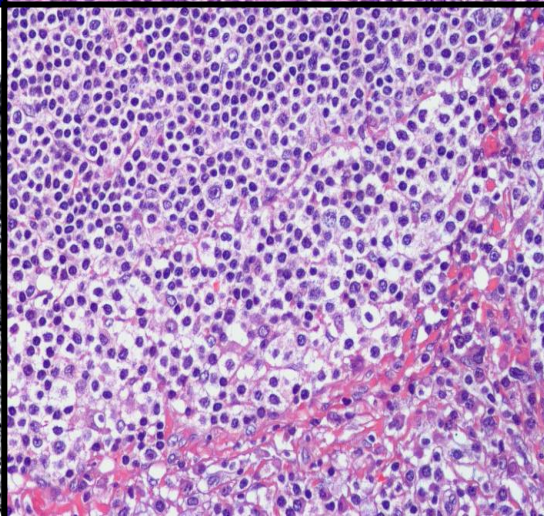
defined, moderately abundant pale cytoplasm. The pattern of lymph node involvement in all 3 cases was predominantly sinusoidal and interfollicular. The neoplastic lymphoid cells were strongly positive for B-cell-restricted antigens; the light- and heavy-chain phenotypes were κ-IgM (2 cases) and κ-IgG (1 case). In all 3 cases,

Am J Pathol 1986; 124: 310-18

MONOCYTOID B-CELL LYMPHOMA 3

ytoid B cell





Citologia e Istologia

- Piccole cellule; citoplasma scarso; nuclei centrocito simili, tondi vs modicamente irregolari
- Possibili aspetti simil-monocitoidi e in un terzo dei casi morfologia plasmacitoide (tipica in cute e tiroide)
- Espansione della zona marginale con progressiva sostituzione dei follicoli B cellulari;
- Lesioni linfoepiteliali: aggregati di ≥3 cellule neoplastiche con distorsione o distruzione dell'epitelio