Cancer Association of South Africa (CANSA)

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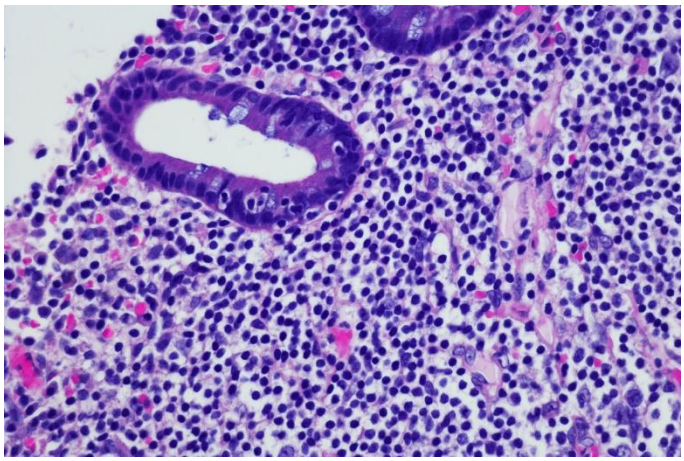
Fact Sheet
on
Nodal Marginal Zone Lymphoma

Introduction

Lymphoma is a type of cancer. It can happen when growth of a lymphocyte (white blood cell) population goes out of control. Marginal zone lymphomas develop from B lymphocytes (B cells) that are normally found in the 'marginal zone'. The marginal zone is at the edge of the area of lymphoid tissue and is where B cells are normally found.



[Picture Credit: NMLZ]

Lymphoid tissue is part of the immune system, for example the lymph nodes or spleen.

Other types of marginal zone lymphomas are MALT Lymphoma (extranodal marginal zone lymphoma) and splenic marginal zone lymphoma.

Nodal Marginal Zone Lymphoma

Nodal marginal zone lymphoma (nodal MZL) is a rare type of low-grade (slow-growing) non-Hodgkin's Lymphoma (NHL). It is a rare type of lymphoma – fewer than 2 in 100 cases of NHL are Nodal Marginal Zonal Lymphoma.

Two clinicopthological forms of Nodal Marginal Zone Lymphoma are recognised: adult type and paediatric-type. Nodal Marginal Zone Lymphomas show overlapping features with other types of Marginal Zone Lymphoma, but distinctive features as well. It remains an enigmatic entity with accompanying difficulties in diagnosis and a lack of knowledge of prognosis and treatment.

Nodal marginal zone lymphoma is more common in older adults. People with this disease are usually diagnosed when they are 60 years old or older. It is more common in women than in men. More than 70% of people are stage 3 or 4 at the time of diagnosis.

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Bron, D., Meuleman, N. & Eurobloodnet for rare diseases and EHA SWG 'Aging and Hematology'. 2019.
PURPOSE OF REVIEW: Choosing an optimal treatment in older patients with indolent lymphomas is a challenge for hematooncologists. They must concomitantly treat some potentially curable entities, manage other symptomatic incurable diseases and protect their patients from life-threatening toxicities. Specific recommendations for older patients with different subtypes of marginal zone lymphomas are thus required in terms of treatment and supportive care.
RECENT FINDINGS: All the data in the literature agree that the therapeutic approach of older patients with malignant hemopathies should include the appraisal of their life expectancy and of the prognostic factors of their tumor, the evaluation of their physiological and cognitive functions and their socioeconomic environment, and their expectancy in terms of quality of life. Major progresses have, therefore, been achieved in the management of lymphoma patients of 80 years and older.
SUMMARY: With an optimal 'geriatric assessment', most of the recommended treatments are also appropriate in older marginal zone lymphoma patients. Extranodal MALT lymphoma: eradication of the pathogen is a major part of the first-line therapy. Prognosis is excellent in early stages. In advanced stages, observation and anti-CD20 antibodies with or without cytostatic drugs are recommended. Nodal MZL: Usually confined to lymph nodes, bone marrow and peripheral blood, they should be managed as follicular lymphomas. Splenic MZL: in this unique entity involving the spleen, the bone marrow and the peripheral blood. Hepatitis infection should be eradicated before considering treatment. Only symptomatic patients require to be treated by splenectomy and/or anti-CD20 antibodies.

Magro, C.M., Momtahen, S., Coleman, M. & Grossman, M.E. 2019.
"Epidermotropic B cell lymphoma represents a rare form of marginal zone lymphoma presenting as a disseminated skin rash resembling pityriasis rosea. To date there are 8 reported cases. In addition to the widespread nature of the skin rash, there is a proclivity for spleen and bone marrow involvement raising consideration regarding its categorization as a systemic lymphoma. We present an 89-year-old man with epidermotropic B cell lymphoma, who presented with a pityriasis rosea-like skin rash. An initial diagnosis of diffuse large cell B cell lymphoma was made based on the extent of dermal-based large cell infiltration. However, after recognizing the epidermotropic component and the distinctive clinical presentation, a diagnosis of epidermotropic B cell lymphoma was rendered. There was minimal bone marrow involvement based only on flow cytometric analysis, but there was no apparent bone marrow or splenic involvement on routine light microscopic assessment. Remission was = achieved with single agent rituximab chemotherapy and the patient remained symptom free. The neoplastic CD20 positive epidermotropic B lymphocytes expressed CXCR3. Similar to the prior reported cases by the authors, the neoplastic cells expressed CXCR3, a chemokine whose organ and tissue specific ligands could contribute to its relatively indolent clinicalcourse."

Luminari, S., Merli, M., Rattotti, S., Tarantino, V., Marcheselli, L., Cavallo, F., Varettoni, M., Bianchi, B., Merli, F., Tedeschi, A., Cabras, G., Re, F., Visco, C., Torresan Delamain, M., Cencini, E., Spina, M., Ferrero, S., Ferrari, A., Deodato, M., Mannina, D., Annibali, O., Rago, A., Orsucci, L., Defrancesco, I., Frigeni, M., Cesaretti, M. & Arcaini, L. 2019.
"Marginal zone lymphomas (MZLs) are indolent nonfollicular B-cell lymphomas (INFLs) and have heterogeneous clinical behavior. Recently, time to progression of disease at 24 months (POD24) was identified to stratify overall survival (OS) in follicular non-Hodgkin lymphoma and in INFL. Here, we examined the ability of POD24 to predict subsequent OS in a large, international cohort of MZL as part of the NF10 prospective international registry headed by Fondazione Italiana Linfomi (FIL). POD24 was only calculated for MZL patients requiring immediate therapy and was defined as experiencing lymphoma progression within 24 months from diagnosis. Among the 1325 patients enrolled in the NF10 study, we identified 321 patients with MZL for whom immediate therapy was planned right after lymphoma diagnosis. Overall, POD24 was confirmed in 59 patients (18%). Three-year OS for patients with POD24 was 53% with a hazard ratio of 19.5 (95% confidence interval,

8.4-45) compared with patients without POD24 (3-year OS, 95%). Association of POD24 with OS was confirmed for the subgroup of splenic and extranodal MZLs. Assessment of POD24 stratifies subsequent outcome in MZL and identifies a high-risk population. This trial was registered at www.clinicaltrials.gov as #NCT02904577."

Incidence of Nodal Marginal Zone Lymphoma

The National Cancer Registry (2017) does not provide any information regarding the incidence of Nodal Marginal Zone Lymphoma.

Signs and Symptoms of Nodal Marginal Zone Lymphoma

The most common symptom is a painless swelling in the neck, armpit or groin. This is caused by the lymphoma cells building up in the lymph nodes, making them bigger.

Other symptoms may include:

- tiredness
- unexplained weight loss
- drenching night sweats
- high temperatures (fevers).

Diagnosis of Nodal Marginal Zone Lymphoma

Nodal Marginal Zone Lymphoma (NMZL) is frequently a diagnosis of exclusion, including reactive hyperplasia and indolent small B cell lymphoma. Morphologically, the tumour cells surround reactive follicles and expand into the interfollicular areas. Follicular colonisation may be present. In cases with a diffuse pattern, follicle remnants may be detected with stains for follicular dendritic cells and germinal centre markers.

In paediatric NMZL, the tumour is similar to that seen in adults except that there are often progressively transformed germinal centres in which the outer border of the follicles is disrupted and infiltrated by tumour cells.

Egan, C., Laurent, C., Alejo, J.C., Pileri, S., Campo, E., Swerdlow, S.H., Piris, M., Chan, W.C., Warnke, R., Gascoyne, R.D., Xi, L., Raffeld, M., Pittaluga, S. & Jaffe, E.S. 2020.

"The diagnosis of nodal marginal zone lymphoma (NMZL) can be challenging, with the differential diagnosis including other low-grade B-cell lymphomas, reactive hyperplasia, and even some cases of peripheral T-cell lymphoma (PTCL). PTCL may have a perifollicular growth pattern mimicking NMZL. We and others have noted an atypical distribution of T-follicular helper (TFH) cells in some cases of NMZL. This study was prompted by the diagnosis of NMZL in several cases in which a marked increase of TFH cells, as determined by staining for programmed death-1 (PD1), had prompted suspicion for a diagnosis of PTCL. We analyzed PD1 staining in 48 cases of NMZL to characterize the extent and pattern of the PD1-positive infiltrate. Three main patterns of PD1 staining were identified: follicular pattern (peripheral, n=16; central, n=9; mixed, n=3), diffuse pattern (n=4), and a reduced or normal staining pattern in residual follicles (n=16). A comprehensive analysis of other TFH markers was undertaken in 14 cases with a high content of PD1-positive cells that were confirmed as B-cell lymphoma by clonality analysis. We describe in detail 5 of these cases in which PTCL was an initial consideration. This study illuminates the diverse immunohistochemical patterns encountered in NMZL and highlights a diagnostic pitfall important for diagnostic accuracy."

Treatment of Nodal Marginal Zone Lymphoma
Experts do not really know how best to treat nodal marginal zone lymphoma. One may be offered one or more of the following treatments:

Watchful waiting (also called active surveillance) - may be an option because nodal marginal zone lymphoma develops slowly and may not need to be treated right away. The healthcare team will monitor the person with nodal marginal zone lymphoma carefully and start treatment when symptoms appear or there are signs that the disease is progressing more quickly.

Chemotherapy - Nodal marginal zone lymphoma usually responds well to chemotherapy. It may be given as a single drug or a combination of drugs and is often given with a targeted therapy drug.

Targeted therapy - uses drugs to target specific molecules (such as proteins) on the surface of cancer cells. These molecules help send signals that tell cells to grow or divide. By targeting these molecules, the drugs stop the growth and spread of cancer cells while limiting harm to normal cells.

Immunotherapy - helps to strengthen or restore the immune system's ability to fight cancer.

Radiation therapy - External beam radiation therapy may be given to the lymph nodes to treat early stage (stage 1 or stage 2) nodal marginal zone lymphoma. It is used when this type of lymphoma affects only 1 or 2 areas of lymph nodes in the body.

De Luca, M.L., Lomnardi, L., Tartaglia, G., Fazio, F., Di Prima, A., Serrao, A., Canichella, M. & Pulsoni, A. 2019. "Many epidemiological, biological and therapeutic studies have extensively investigated the etiological link between HCV infection and B-cell Non-Hodgkin Lymphoma (NHL). Large experiences in the literature demonstrated HCV-related indolent NHL regression after antiviral therapy. While the response to interferon-ribavirin-based antiviral therapy is well documented, evidence of the efficacy of interferon-free Direct-Acting Antivirals (DAAs) in this subset of lymphoma is also currently increasing. Splenic and Nodal Marginal zone Lymphoma (MZL) are frequently associated with HCV chronic infection. In this article we report two cases of HCV-related MZL with an unusual presentation, subcutaneous "lipoma-like" nodules, treated with DAAs. Both patients, a 59-years-old woman and a 72-years-old man, were affected by HCV chronic infection since several years and were referred to our Institute for a diagnosis of MZL with subcutaneous presentation. Given the possible etiological link with HCV infection, both patients were treated with DAAS. A Sustained virological response (SVR) was reached after few weeks of therapy and at the end of treatment a clinically and radiologically documented reduction of MZL localizations, persisting to date, were obtained in both patients. The two clinical cases presented in this article confirm the efficacy of DAA's as first-line treatment in HCV related NHL, also in this rare entity of MZL with subcutaneous presentation."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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"Advanced marginal zone lymphoma (MZL) is an incurable B-cell malignancy dependent on B-cell receptor signaling. The phase 2 PCYC-1121 study demonstrated the safety and efficacy of single-agent ibrutinib 560 mg/d in 63 patients with relapsed/refractory MZL treated with prior rituximab (RTX) or rituximab-based chemoimmunotherapy (RTX-CIT). We report the final analysis of PCYC-1121 with median follow-up of 33.1 months (range: 1.4-44.6). Overall response rate (ORR) was 58%; median duration of response (DOR) was 27.6 months (95% confidence interval [CI]: 12.1 to not estimable [NE]); median progression-free survival (PFS) was 15.7 months (95% CI: 12.2-30.4); and median overall survival (OS) was not reached (95% CI: NE to NE). Patients with prior RTX treatment had better outcomes (ORR: 81%; median DOR: not reached [95% CI: 12.2 to NE]; median PFS: 30.4 months [95% CI: 22.1 to NE]; median OS: not reached [95% CI: 30.3 to NE]) vs those with prior RTX-CIT treatment (ORR: 51%; DOR: 12.4 months [95% CI: 2.8 to NE]; PFS: 13.8 months [95% CI: 8.3-22.5]; OS: not reached [95% CI: NE to NE]). ORRs were 63%, 47%, and 62% for extranodal, nodal, and splenic subtypes, respectively. With up to 45 months of ibrutinib treatment, the safety profile remained consistent with prior reports. The most common grade ≥3 event was anemia (16%). Exploratory biomarker analysis showed NF-κB pathway gene mutations correlated with outcomes. Final analysis of PCYC-1121 demonstrated long-term safety and efficacy of ibrutinib in patients with relapsed/refractory MZL, regardless of prior treatment or MZL subtype. This trial was registered at www.clinicaltrials.gov as #NCT01980628."

Medical Disclaimer

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NMLZ
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