Follicular Lymphoma and Primary Splenic Lymphoma

Subjects: Hematology

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Follicular lymphoma (FL) is a mature B-cell non-Hodgkin lymphoma derived from germinal center B-lymphocytes (centrocytes and centroblasts) that generally has at least a partially follicular/nodular histologic pattern.

Keywords: follicular lymphoma

1. Background

Primary splenic lymphoma (PSL) is a rare malignancy representing about 1% of all lymphoproliferative disorders, when using a strict definition that allows only involvement of spleen and hilar lymph nodes. In contrast, secondary low-grade B-cell lymphomas in the spleen, such as follicular lymphomas (FL), lymphoplasmacytic lymphoma and chronic lymphocytic leukemia/ small lymphocytic lymphoma, particularly as part of advanced stage disease, are more common. Indolent B cell lymphomas expressing CD10 almost always represent FL.

2. Epidemiology of Follicular Lymphoma

PSL comprise approximately 1% of all malignant neoplasms [1][2], when the disease is restricted to involvement of the spleen and hilar lymph nodes. However, a broader definition also encompassing liver, bone marrow or peripheral blood involvement, but lacking prominent distant adenopathy, is accepted as well.

Epidemiologically, one study showed the prevalence of PSL to be approximately 62%, where DLBCL was the most common lymphoid neoplasm (25%) followed by splenic MZL (15%) and FL (6%) [3]. Low-grade CD10-positive lymphoproliferative disorders encountered in splenic specimens belong most frequently to the category of FL (either primary or secondary). However, a subset of FL in the spleen represents aggressive disease (equivalent to DLBCL), considering that extranodal FL is most commonly a high-grade lymphoma that may lack expression (or translocation) of BCL2 [4][5]. However, duodenal-type FL represents an exception to this rule, due to an indolent course and constant expression of BCL2 [6].

The incidence of PSFL is unknown and may be overestimated because the vast majority of FL in the spleen represent secondary disease. In general, PSFL accounts for a small fraction of PSL and only a few case series are available on this entity [7][8][9].

In general, FL has an incidence of 2.1 per in the United States (SEER Follicular Lymphoma—Cancer Stat Facts (https://seer.cancer.gov/statfacts/html/follicular.html, accessed 16 October 2021), and is less common in eastern Europe, Asia and developing countries [10]. FL is 2–3 times more common in white than in black patients [6][11], and disproportionately affects females. The mean age at diagnosis (including all histologic grades) has been estimated to be 68 years, which is similar to nodal FL [7][8][12][13][14]. PSFL is rarely seen in patients younger than 50 years based on case series [7][8][13].

3. Clinical Presentation

Due to the rarity of PSFL, clinical features are incompletely defined. In contrast to nodal FL, most patients present with stage I/II disease [14]. A minority of cases show bone marrow, peripheral blood or liver infiltration [8]. In PSFL, isolated splenomegaly either asymptomatic or accompanied by upper abdominal discomfort is the rule [8]. B symptoms occur in a minority (less than 20%) of cases. Cytopenias (anemia and/or thrombocytopenia) secondary to hypersplenism or rarely due to bone marrow infiltration have been reported [8][13]. In contrast, nodal FL, which may involve the spleen, is usually accompanied by distant lymphadenopathy and more frequent systemic symptoms. The real frequency of PSFL remains to be established. As such, the disease may be incidentally found during work up for other medical conditions [15]. However, pathologic splenic rupture due to massive splenomegaly has been described [16]. Atypical lymphocytosis observed in

peripheral blood smears or liver biopsies and/or mild to moderate splenomegaly may be identified incidentally during clinical encounters unrelated to lymphoma work-up in asymptomatic or paucisymptomatic patients. Interestingly, anti-hepatitis C virus (HCV) antibodies were more prevalent in patients with splenic FL compared with nodal FL with splenic infiltration in a study of 17 cases [8].

4. Treatment and Prognosis

Treatment of splenic lymphomas is ascribed to its lineage. Based on a few available studies it has been suggested to treat patients with splenic lymphomas with regimens developed for nodal lymphomas, which is particularly true for FL. However, long term outcome data are unavailable given the rarity of splenic lymphomas. Consequently, specific treatment modalities are not formally recommended for PSFL yet [17].

HCV infection has been more frequently described in PSFL than in nodal FL [8], and anti-viral therapy alone can induce remission of lymphoproliferative disorders [18][19][20], suggesting this option for PSFL.

Stage I PSFL diagnosed on splenectomy specimen could be subjected to an active observation/expectant management strategy, mirroring guidelines for nodal FL stage I treated with complete surgical removal of the affected lymph nodes [17]. Long treatment-free intervals may be achieved by this approach, while minimizing therapy-related adverse effects. A recent large case series of splenic lymphomas undergoing splenectomy demonstrated that additional chemotherapy after surgery did not impact overall survival (OS) in FL [14], further supporting the practice of expectant management. However, the management of stage I nodal FL remains mired in controversy. While current guidelines still recommend localized radiotherapy, heterogenous alternatives (ranging from vigilance to adjuvant Rituximab monotherapy or immunochemotherapy) are used as evident from prospective observational studies and real-world series [21]. The combination of radiotherapy with systemic treatments (chemotherapy or immunochemotherapy) has been shown to prolong PFS but not OS, and the decision to offer additional treatment remains both patient and physician dependent [22][23]. These concepts have been applied to early PSFL. On the other hand, PSFL presenting with combinations of liver, bone marrow and peripheral blood involvement are expected to behave like advanced FL (stage IV), and the therapeutic choices range from active observation (for low tumor burden asymptomatic disease) to first line immunochemotherapy (for high tumor burden symptomatic disease) [17]. Commonly, combinations of Rituximab with Bendamustine, CHOP or CVP have been used as first line regimens [24][25]. Recently, substituting Rituximab for Obinutuzumab (a type II glycoengineered humanized anti-CD20 monoclonal antibody) in similar chemotherapy combinations was shown to prolong PFS without impacting OS [26].

Maintenance regimens with anti-CD20 monoclonal antibodies have been applied by several investigators, again prolonging PFS but not OS [27]. The efficacy of maintenance regimens for advanced leukemic disease (as is common in stage IV PSFL) deserves investigation, since lymphocytosis at presentation implies poor prognosis in nodal FL [28][29]. Treatment of relapsed PSFL can also be modelled on nodal FL, where management is influenced by multiple, patient and disease related factors, including the interval between diagnosis and relapse, and documentation of histologic transformation. A growing number of signaling pathway-specific/non-chemotherapy agents and cellular therapies are becoming available for FL, which could change the course of this still incurable disease [30][31]. However, the applicability of these new strategies to PSFL is unknown, and probably dependent on further clarification of specific biological characteristics and pathogenic mechanisms.

Conclusive data on prognostication of PSFL are not available yet. In the largest series published to date, survival was similar to nodal FL using treatment options ranging splenectomy alone to combined surgery and chemotherapy [13]. It is conceivable that the prognosis of PSFL may be influenced by the stage of disease and prognostic scores usually applied to nodal FL (namely the Follicular Lymphoma International Prognostic Index/FLIPI and FLIP2) [32][33]. However, the clinical outcomes of patients with spleen-confined disease have been similar to those of individuals with disseminated lymphoma [7], which may be explained by a limited sample size.

When PFSL transforms to aggressive lymphoma, regimens for DLBCL (immunochemotherapy with anti-CD20 antibodies and standard anthracycline-based chemotherapy for at least four cycles in localized stages) are used achieving comparable results.

References

1. Gobbi, P.G.; Grignani, G.E.; Pozzetti, U.; Bertoloni, D.; Pieresca, C.; Montagna, G.; Ascari, E. Primary splenic lymphoma: Does it exist? Haematologica 1994, 79, 286–293.
2. Healy, N.A.; Conneely, J.B.; Mahon, S.; O'Riardon, C.; McAnena, O.J. Primary splenic lymphoma presenting with ascites. Rare Tumors 2011, 3, 81–82.
3. Shimizu-Kohno, K.; Kimura, Y.; Kiyasu, J.; Miyoshi, H.; Yoshida, M.; Ichikawa, R.; Niino, D.; Ohshima, K. Malignant lymphoma of the spleen in Japan: A clinicopathological analysis of 115 cases. Pathol. Int. 2012, 62, 577–582.
4. Özsan, N.; Bedke, B.J.; Law, M.E.; Inwards, D.J.; Ketterling, R.P.; Knudson, R.A.; Keeney, G.L.; Dogan, A.; Feldman, A.L. Clinicopathologic and genetic characterization of follicular lymphomas presenting in the ovary reveals 2 distinct subgroups. Am. J. Surg. Pathol. 2011, 35, 1691–1699.
5. Vang, R.; Medeiros, L.J.; Ha, C.S.; Deavers, M.T. Non-Hodgkin's lymphomas involving the uterus: A clinicopathologic analysis of 26 cases. Mod. Pathol. 2000, 13, 19–28.
6. Swerdlow, S.H.; Campo, E.; Harris, N.L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J. (Eds.) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised, 4th ed.; IARC: Lyon, France, 2017.
7. Howard, M.T.; Dufresne, S.; Swerdlow, S.H.; Cook, J.R. Follicular lymphoma of the spleen: Multiparameter analysis of 16 cases. Am. J. Clin. Pathol. 2009, 131, 656–662.
8. Shimono, J.; Miyoshi, H.; Kamimura, T.; Eto, T.; Miyagishima, T.; Sasaki, Y.; Kurita, D.; Kawamoto, K.; Nagafuji, K.; Seto, M.; et al. Clinicopathological features of primary splenic follicular lymphoma. Ann. Hematol. 2017, 96, 2063–2070.
9. Jhuang, J.Y.; Hsieh, Y.C.; Kuo, C.C.; Su, Y.Z.; Chuang, S.S. Primary splenic low-grade follicular lymphoma presenting with leukaemia and large cell transformation in the marrow. Pathology 2017, 49, 649–652, Erratum in 2017, 49, 819.
10. Jasionowski, T.M.; Hartung, L.; Greenwood, J.H.; Perkins, S.L.; Bahler, D.W. Analysis of CD10+ hairy cell leukemia. Am. J. Clin. Pathol. 2003, 120, 228–235.
11. Le, M.; Ghazawi, F.; Alakel, A.; Netchiporouk, E.; Rahme, E.; Zubarev, A.; Powell, M.; Moreau, L.; Roshdy, O.; Glassman, S.J.; et al. Incidence and Mortality Trends and Geographic Patterns of Follicular Lymphoma in Canada. Curr. Oncol. 2019, 26, 473–481.
12. Junlén, H.R.; Peterson, S.E.; Kimby, E.; Lockmer, S.; Linden, O.; Nilssonehle, H.; Erlanson, M.; Hagberg, H.; Rådlund, A.; Hagberg, O.; et al. Follicular lymphoma in Sweden: Nationwide improved survival in the rituximab era, particularly in elderly women: A Swedish Lymphoma Registry study. Leukemia 2015, 29, 668–676.
13. Mollejo, M.; Rodríguez-Pinilla, M.S.; Montes-Moreno, S.; Algara, P.; Dogan, A.; Cigudosa, J.C.; Juarez, R.; Flores, T.; Forteza, J.; Arribas, A.; et al. Splenic follicular lymphoma: Clinicopathologic characteristics of a series of 32 cases. Am. J. Surg. Pathol. 2009, 33, 730–738.
14. Fallah, J.; Olszewski, A.J. Diagnostic and therapeutic splenectomy for splenic lymphomas: Analysis of the National Cancer Data Base. Hematology 2019, 24, 378–386.
15. Matsuda, I.; Okada, M.; Inoue, T.; Tokugawa, T.; Ogawa, H.; Hirota, S. Primary follicular lymphoma of the spleen incidentally found in a patient with alcohol- and hepatitis C-related liver cirrhosis. Int. J. Clin. Exp. Pathol. 2014, 7, 4484–4488.
16. Dayama, A.P.; Kapoor, R.; Dass, J.; Singh, G.; Mahapatra, M.; Pati, H. Pathologic splenic rupture in a patient with follicular lymphoma. Mediterr. J. Hematol. Infect. Dis. 2011, 3, e2011051.
17. Dreyling, M.; Ghielmini, M.; Rule, S.; Salles, G.; Ladetto, M.; Tonino, S.; Herfarth, K.; Seymour, J.; Jerkeman, M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2021, 32, 298–308.
18. Maciocia, N.; O'Brien, A.; Ardeshna, K. Remission of Follicular Lymphoma after Treatment for Hepatitis C Virus Infection. N. Engl. J. Med. 2016, 375, 1699–1701.
19. Arcaini, L.; Besson, C.; Frigeni, M.; Fontaine, H.; Goldaniga, M.; Casato, M.; Visentini, M.; Torres, H.A.; Loustaud-Ratti, V.; Peveling-Oberhag, J.; et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood 2016, 128, 2527–2532.
20. Alric, L.; Besson, C.; Lapidus, N.; Jeannel, J.; Michot, J.-M.; Cacoub, P.; Canioni, D.; Pol, S.; Davi, F.; Rabiega, P.; et al. Antiviral Treatment of HCV-Infected Patients with B-Cell Non-Hodgkin Lymphoma: ANRS HC-13 Lympho-C Study. PLoS ONE 2016, 11, e0162965.
21. Friedberg, J.W.; Taylor, M.D.; Cerhan, J.; Flowers, C.R.; Dillon, H.; Farber, C.M.; Rogers, E.S.; Hainsworth, J.D.; Wong, E.K.; Vose, J.M.; et al. Follicular lymphoma in the United States: First report of the national lymphocare study. J. Clin. Oncol. 2009, 27, 1202–1208.

22. MacManus, M.; Fisher, R.; Roos, D.; O'Brien, P.; Macann, A.; Davis, S.; Tsang, R.; Christie, D.; McClure, B.; Joseph, D.; et al. Randomized Trial of Systemic Therapy after Involved-Field Radiotherapy in Patients with early-Stage Follicular Lymphoma: TROG 99.03. J. Clin. Oncol. 2018, 36, 2918–2925.
23. Advani, R.; Rosenberg, S.A.; Horning, S.J. Stage I and II follicular non-Hodgkin's lymphoma: Long-term follow-up of no initial therapy. J. Clin. Oncol. 2004, 22, 1454–1459.
24. Marcus, R.; Imrie, K.; Solal-Celigny, P.; Catalano, J.V.; Dmoszynska, A.; Raposo, J.C.; Offner, F.C.; Gomez-Codina, J.; Belch, A.; Cunningham, D.; et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J. Clin. Oncol. 2008, 26, 4579–4586.
25. Hiddemann, W.; Kneba, M.; Dreyling, M.; Schmitz, N.; Lengfelder, E.; Schmits, R.; Reiser, M.; Metzner, B.; Harder, H.; Hegewisch-Becker, S.; et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005, 106, 3725–3732.
26. Marcus, R.; Davies, A.; Ando, K.; Klapper, W.; Opat, S.; Owen, C.; Phillips, E.; Sangha, R.; Schlag, R.; Seymour, J.F.; et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N. Engl. J. Med. 2017, 377, 1331–1344.
27. Salles, G.A.; Seymour, J.F.; Feugier, P.; Offner, F.; Lopez-Guillermo, A.; Belada, D.; Xerri, L.; Bouabdallah, R.; Catalano, J.; Brice, P.; et al. Long term follow-up of the PRIMA study: Half of patients receiving rituximab maintenance remain progression free at 10 years. Blood 2017, 130 (Suppl. S1), 486.
28. Sarkozy, C.; Baseggio, L.; Feugier, P.; Callet-Bauchu, E.; Karlin, L.; Seymour, J.F.; Lebras, L.; Michallet, A.-S.; Offner, F.; Dumas, O.; et al. Peripheral blood involvement in patients with follicular lymphoma: A rare disease manifestation associated with poor prognosis. Br. J. Haematol. 2013, 164, 659–667.
29. Sarkozy, C.; Seymour, J.F.; Ferme, C.; Caballero, L.; Ghesquieres, H.; Leppä, S.; Delarue, R.; Pedersen, L.M.; Mounier, C.; da Silva, M.G.; et al. Rituximab maintenance obviates the poor prognosis associated with circulating lymphoma cells in patients with follicular lymphoma. Blood 2014, 123, 2740–2742.
30. Apostolidis, J.; Mokhtar, N.; Al Omari, R.; Darweesh, M.; Al Hashmi, H. Follicular lymphoma: Update on management and emerging therapies at the dawn of the new decade. Hematol. Oncol. 2020, 38, 213–222.
31. Matasar, M.J.; Luminari, S.; Barr, P.M.; Barta, S.K.; Danilov, A.V.; Hill, B.T.; Phillips, T.J.; Jerkeman, M.; Magagnoli, M.; Nastoupil, L.J.; et al. Follicular lymphoma: Recent and emerging therapies, treatment strategies, and remaining unmet needs. Oncologist 2019, 24, e1236–e1250.
32. Solal-Céligny, P.; Roy, P.; Colombat, P.; White, J.; Armitage, J.O.; Arranz-Saez, R.; Au, W.Y.; Bellei, M.; Brice, P.; Caballero, D.; et al. Follicular lymphoma international prognostic index. Blood 2004, 104, 1258–1265.
33. Federico, M.; Bellei, M.; Marcheselli, L.; Luminari, S.; Lopez-Guillermo, A.; Vitolo, U.; Pro, B.; Pileri, S.; Pulsoni, A.; Soubeyran, P.; et al. Follicular lymphoma international prognostic index 2: A new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J. Clin. Oncol. 2009, 27, 4555–4562.