World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i2.26

World J Gastrointest Oncol 2012 February 15; 4(2): 26-29
ISSN 1948-5204 (online)

CASE REPORT

Running in the family: MALT lymphoma and autoimmune disease in mother and daughter

Barbara Kiesewetter, Marlene Troch, Leonhard Müllauer, Markus Raderer

Barbara Kiesewetter, Marlene Troch, Markus Raderer, Departments of Internal Medicine I, Division of Oncology, and the Comprehensive Cancer Center of the Medical University Vienna, A-1090 Vienna, Austria
Leonhard Müllauer, Departments of Internal Medicine I, Division of Pathology, and the Comprehensive Cancer Center of the Medical University Vienna, A-1090 Vienna, Austria
Author contributions: All authors contributed to this manuscript.
Correspondence to: Dr. Markus Raderer, MD, Professor, Department of Internal Medicine I, Division of Onoclogy, and the Comprehensive Cancer Center of the Medical University Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. markus.raderer@meduniwien.ac.at
Telephone: +43-1-40400-2296 Fax: +43-1-40400-2296
Received: April 11, 2011 Revised: September 21, 2011
Accepted: September 28, 2011
Published online: February 15, 2012

Abstract

Gastric B-cell lymphoma of the mucosa associated lymphoid tissue (MALT) lymphoma is one of the most common forms of extranodal lymphoma. In addition to infection with *Helicobacter pylori* (*H. pylori*), the presence of an underlying autoimmune disease has also been associated with MALT lymphoma development. To date, no familial predisposition for MALT lymphomas has been reported as opposed to other types of lymphoma. A 65-year-old woman was admitted at our institution in 1998 with a diagnosis of *H. pylori* positive gastric MALT lymphoma and the presence of chronic autoimmune thyroiditis was established on further work-up. *H. pylori* eradication did not result in regression of the lymphoma and RT-PCR showed the presence of the t(11;18)(q21;q21) translocation. About 1.5 years after *H. pylori* eradication, chemotherapy with cladribine resulted in complete remission. Due to lymphoma recurrence 13 mo later, radiotherapy to the stomach (46 Gy) resulted in minimal residual disease without further progression. The patient developed a second malignancy (Epstein-Bar virus-associated anaplastic large cell lymphoma in the mediastinum) in 2004 which initially responded to two courses of chemotherapy, but she refused further therapy and died of progressive lymphoma in 2006. In 2008, her 55 years old daughter with a long standing Sjögren's syndrome was diagnosed with MALT lymphoma of the right parotid, but no evidence of gastric involvement or *H. pylori* infection was found. Currently, she is alive without therapy and undergoing regular check-ups. To our knowledge, this is the first report of MALT lymphoma in a first-degree relative of a patient with gastric MALT lymphoma in the context of two autoimmune diseases without a clearly established familial background.

Key words: Mucosa associated lymphoid tissue lymphoma; *Helicobacter pylori*; Autoimmunity; Familial lymphoma

Peer reviewer: Marius Raica, Professor, Department of Histology and Cytology, "Victor Babes" University of Medicine and Pharmacy, Pta Eftimie Murgu 2, 300041, Timisoara, Romania

Kiesewetter B, Troch M, Müllauer L, Raderer M. Running in the family: MALT lymphoma and autoimmune disease in mother and daughter. *World J Gastrointest Oncol* 2012; 4(2): 26-29 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i2/26.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i2.26

INTRODUCTION

Malignant lymphomas are tumors with an increasing incidence. Despite wide geographic variations, the overall incidence is currently estimated at 2/100 000[1]. As opposed to solid tumors, however, malignant lymphomas constitute a heterogeneous group of different disease entities. In view of this, an explanation for the rising incidence

is difficult, as various types of lymphomas have distinct characteristics and contributing pathogenetic factors. In general, the presence of an autoimmune disease has been judged to be risk factor for the development of malignant lymphomas and Sjögren's syndrome (SS), rheumatoid arthritis, autoimmune thyroiditis and Lupus erythematosus have especially been associated with the development of diffuse large B-cell lymphomas, extranodal marginal B-cell lymphomas of the mucosa associated lymphoid tissue (MALT lymphoma), but also Hodgkin's disease[2-4]. Controversially, immunosuppression has also been linked to lymphoma development, as evidenced by patients with post-transplant lymphoproliferative diseases and patients being given immunosuppression for rheumatoid diseases. In the latter, however, there is still some controversy as to whether lymphoma development is de facto linked to the underlying disease necessitating immunosuppression rather than the immunosuppressive agents[5,6].

A familial background of non-Hodgkin's lymphoma (NHL) has repeatedly been reported to constitute a significant risk factor for lymphoma development. In an evaluation of first-degree relatives of lymphoma patients, Paltiel *et al*[7] observed an increased rate of both NHL as well as Hodgkin's lymphoma development among the population when compared to control groups. The Swedish Family Cancer database analyzed familial risk for NHL in terms of histopathological subtypes and showed a significantly increased risk for diffuse large B-cell lymphomas and follicular lymphomas[8].

MALT lymphoma is among the more common lymphoma subtypes and constitutes about 7%-8% of all newly diagnosed B-cell lymphomas[9]. In terms of pathogenesis, gastric MALT lymphoma is the paradigm for an immunomediated malignancy, as evidenced by the strong association with SS, autoimmune thyroiditis and, in case of gastric MALT lymphoma, infection with *Helicobacter pylori* (*H. pylori*)[10]. The validity of the latter model/association has been demonstrated by the impressive response of gastric MALT lymphomas to eradication of the bacteria, resulting in complete remissions in up to 80% of selected patients[11,12]. Apart from autoimmunity and chronic antigenic stimulation driven by infections, however, no risk factors for MALT lymphoma have been reported, and no evidence for familial clustering of MALT lymphomas can be found in the current literature.

We report the cases of two women (mother and daughter), who both developed MALT lymphoma with the background of an autoimmune disease.

CASE REPORT

A 65-year-old woman was admitted at our institution for further treatment of a recently diagnosed gastric MALT lymphoma in September 1998. Due to epigastric complaints for a period of about five mo, a gastroscopy was performed, which disclosed the presence of a gastric ulcer in the corpus. Multiple biopsies from the ulcer as well as from the surrounding hyperemic mucosa were taken, and disclosed the presence of extranodal marginal zone MALT lymphoma along with active infection with *H. pylori*. Antibiotic therapy with clarithromycin, metronidazole for 10 d and intake of pantoprazole were initiated. At our institution, a re-gastroscopy was performed 6 wk after eradication therapy, showing no evidence of *H. pylori* and healing of the ulcer, but unchanged histological presence of MALT lymphoma. RT-PCR performed on paraffin embedded specimens showed the presence of the MALT lymphoma specific t(11;18)(q21;q21)-translocation.

The patient's initial physical condition was good and blood counts were normal except an elevated β2-microglobulin level (2.73 mg/L) and anemia grade I related to slight chronic blood loss from the gastritis. The medical history revealed appendectomy, cholecystectomy and hysterectomy and the familial history was positive for malignancies (mother died age 38 years from what the patient related as "acute leukemia" and a brother had died from pancreatic carcinoma). At the time of admission, the medical history of both the patient's daughters was uneventful, except SS in the older daughter which had been histologically verified in 1993. Extensive staging including endosonography of the stomach and duodenum, colonoscopy with multiple biopsies, 18F-FDG-PET, CT-scan of thorax and abdomen, ultrasound of lymph nodes, thyroid and salivary glands as well as a bone marrow biopsy showed restriction of the lymphoma to the stomach, corresponding to stage I disease. Thyroid ultrasound, however, was suggestive of chronic autoimmune thyroiditis, which was also verified by the presence of elevated thyroid autoantibodies with subclinical hypothyreosis (TSH 8.9 mU/L and thyreoglobulin-autoantibodies 424 ng/mL).

Consecutive serial gastroscopies performed every three mo showed no chance of the MALT lymphoma infiltrate 1.5 years after initial diagnosis and chemotherapy with the nucleoside analogue cladribine was initiated. Treatment consisted of 0.12 mg/kg cladribine given i.v. days 1-5 every 28 d for four courses, resulting in complete remission (CR) of the gastric MALT lymphoma.

Thirteen months after initial CR, a control gastroscopy disclosed histological evidence for *H. pylori*-negative, t(11;18)(q21;q21)-positive relapse of gastric MALT lymphoma and endosonography showed enlarged lymph nodes along the lesser curvature. Consequently, the patient received radiotherapy at a dose of 46 Gy and again achieved a histologically verified CR. Upon the third follow-up gastroscopy, however, the presence of probable minimal residual disease (pMRD) was suspected and the CR was rated as a probable sampling error. All gastroscopies until the patient's death repeatedly disclosed pMRD without progression in spite of the fact that no therapy was given.

In July 2004, the patient developed acute dyspnea and a CT scan showed a subglottic mass leading to massive tracheal compression. Histological assessment showed the presence of anaplastic large B-cell lymphoma associated with Epstein-Bar virus. Molecular assessment

disclosed the absence of t(11,18)(q21;q21) and no clonal relationship to the initial MALT lymphoma and was thus rated as a second malignancy. Two cycles of chemotherapy were administered containing rituximab, mitoxantrone, cyclophosphamide and vincristine, resulting in complete remission of the lymphoma. The patient, however, refused any further therapy and remained in CR until February 2006, when the patient had to be re-admitted due to rapidly progressing dyspnea and deteriorating general condition, resulting in the patient's death in May 2006.

In February 2008, the patient's daughter was admitted at our institution at the age of 55 years. After having been diagnosed with SS in 1993, she had developed a painless swelling in the right parotid gland. Ultrasound and a consecutive MRI were suggestive of a Warthin tumor and the patient underwent superficial parotidectomy. Upon histological assessment, infiltration of the parotid with MALT lymphoma was found. Apart from the diagnosis of SS with consecutive dryness of eyes and mouth, the patient's general condition was excellent and her medical history uneventful.

The lymphoma was analyzed for MALT lymphoma specific genetic aberrations including RT-PCR for t(11;18)(q21;q21) as well as FISH for t(14;18) involving IGH/MALT and assessment of trisomies 3 and 8, yielding negative results. For staging, a CT scan of thorax and abdomen and MRI of orbit, salivary glands and the cervical region were performed. Findings were inconspicuous except enlarged bilateral lymph nodes measuring up to 22 mm, which were rated as involvement with lymphoma. However, no histological verification of these lymph nodes was done. In view of the mother's medical history, a gastroscopy and a bone marrow biopsy were performed. No evidence of lymphoma involvement was seen on these investigations and the patient was rated negative for *H. pylori* both on histology as well as serology. As the patient was asymptomatic and without documented progression of the disease, she is currently on a wait-and-see strategy with radiological assessment consisting of MRI of salivary glands and cervical region as well as a CT of thorax and abdomen every 3 mo.

DISCUSSION

A familial background of non-Hodgkin lymphoma or other lymphoproliferative malignancies has repeatedly been reported as a significant risk factor for NHL. A computerized literature research identified nine recent analyses, including a total of 21 378 patients with NHL for assessment of familial risk[7,8,13-19]. An analysis of the Swedish Family Cancer Database, including 4.445 patients diagnosed with NHL having at least one first-degree relative diagnosed with NHL, has assessed the familial risk in terms of standardized incidence ratios (SIRs). A first-degree relative suffering from NHL significantly increased the general risk for NHL (SIR = 1.8), with the SIR for diffuse large B-cell lymphoma being 1.8, follicular lymphoma 2.0 and "B-cell lymphoma, not otherwise specified" being 3.4[8].

Wang *et al*[18] evaluated 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium comprising 17 case control studies and reported similar results. The overall NHL risk for a person with a first-degree relative compared to a stratified control collective was reported at an odds ratio (OR) of 1.5. Controversial findings, however, were reported whether a parent or sibling with NHL provides a higher risk for consecutive NHL-development. Furthermore, the level of risk seemed to be higher for histopathological specific concordant neoplasm than for other subtypes in various reports, but due to the limited number of cases, statistical significance was not reached[8,18].

While infectious agents and autoimmune diseases have repeatedly been linked with MALT lymphoma pathogenesis, no data on a familial background in patients with MALT lymphoma have been published so far.

As it is, the case of the patient with gastric MALT lymphoma also highlights various clinically relevant points. First of all, it underscores the potential influence of chronic autoimmune disease on the development of gastric MALT lymphoma, as recently highlighted by Troch *et al*[20]. As has been shown, these lymphomas might be independent of *H. pylori* even at early stages and the presence of an underlying autoimmune disease has been reported as a negative prognostic risk factor for lymphoma regression after *H. pylori* eradication[4]. In addition, the lymphoma cells in our patient harbored the t(11;18)(q21;q21) translocation, which is also thought to confer resistance to antibiotic therapy. Consequently, no response was seen with *H. pylori* eradication and chemotherapy subsequently resulted in complete remission (CR). This CR was nevertheless relatively short and consecutive radiation resulted in pMRD, which was initially erroneously assessed as CR probably due to a sampling error. In spite of the fact that no further therapy was applied, the MALT lymphoma was stable for a prolonged time, i.e., until the patient's death. This is in keeping with recent data published by Fischbach *et al*[21] who have shown that patients with pMRD after *H. pylori*-eradication should not undergo further therapy, as has also been underscored by the recently published EGILS-consensus for management of gastric MALT-lymphoma[22]. To our knowledge, the cases presented in this article constitute the first report of MALT lymphoma developing in first degree relatives. A computerized search of the published literature disclosed no information on MALT lymphoma and a familial background, and "MALT lymphoma" as a distinct lymphoma entity was not listed in the Swedish Family Cancer Database or in any other article related to familial NHL development.

The MALT lymphomas diagnoses in our patients, however, showed different characteristics, as the mother's lymphoma developed in the stomach, while the daughter was diagnosed with parotid MALT lymphoma. As expected in a t(11;18)(q21;q21) positive gastric MALT lymphoma, no response to *H. pylori* eradication was seen and necessitated chemotherapy. In the parotid MALT lymphoma, no

genetic abnormalities could be detected and no evidence of gastric MALT lymphoma or *H. pylori* infection was seen at a staging gastroscopy. Interestingly, both mother and daughter suffered not only from MALT lymphoma but were also diagnosed with an autoimmune disorder (chronic autoimmune thyroiditis in the mother, SS in the daughter).

To date, no familial background for the development of MALT lymphoma has been reported, but our cases nevertheless suggest that the combination of autoimmune disease and MALT lymphoma in a first degree relative might constitute a risk factor for consecutive MALT lymphoma development.

REFERENCES

1 **Jaffe ES**, Harris NL, Stein H, Campo E, Pileri SA, Swerdlow SH. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of the haematopoietic and lymphoid tissues. IARC: Lyon, 2008: 158-166

2 **Ekström Smedby K**, Vajdic CM, Falster M, Engels EA, Martínez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, De Sanjosé S, Chiu BC, Dal Maso L, Cocco P, Maynadié M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE, Cozen W. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008; **111**: 4029-4038

3 **Anderson LA**, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, Berndt SI, Ricker W, Parsons R, Engels EA. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int J Cancer* 2009; **125**: 398-405

4 **Wöhrer S**, Troch M, Streubel B, Zwerina J, Skrabs C, Formanek M, Hauff W, Hoffmann M, Müllauer L, Chott A, Raderer M. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. *Leukemia* 2007; **21**: 1812-1818

5 **Opelz G**, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; **4**: 222-230

6 **Wolfe F**, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; **50**: 1740-1751

7 **Paltiel O**, Schmit T, Adler B, Rachmilevitz EA, Polliack A, Cohen A, Haim N, Shachar MB, Epelbaum R, Barchana M, Cohen R, Ben Yehuda D. The incidence of lymphoma in first-degree relatives of patients with Hodgkin disease and non-Hodgkin lymphoma: results and limitations of a registry-linked study. *Cancer* 2000; **88**: 2357-2366

8 **Altieri A**, Bermejo JL, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. *Blood* 2005; **106**: 668-672

9 **Isaacson PG**, Chott A, Nakumura S, Müller-Hermelink HK, Harris NL, Swerdlow SH. Extranodal marginal cell lymphoma of mucosa-associated tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of the haematopoietic and lymphoid tissues. IARC: Lyon, 2008: 214-219

10 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176

11 **Zullo A**, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, Tomao S, Stolte M, Morini S, Vaira D. Effects of Helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol* 2010; **8**: 105-110

12 **Fischbach W**, Goebeler-Kolve ME, Dragosics B, Greiner A, Stolte M. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive Helicobacter pylori eradication therapy: experience from a large prospective series. *Gut* 2004; **53**: 34-37

13 **Chang ET**, Smedby KE, Hjalgrim H, Porwit-MacDonald A, Roos G, Glimelius B, Adami HO. Family history of hematopoietic malignancy and risk of lymphoma. *J Natl Cancer Inst* 2005; **97**: 1466-1474

14 **Chatterjee N**, Hartge P, Cerhan JR, Cozen W, Davis S, Ishibe N, Colt J, Goldin L, Severson RK. Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1415-1421

15 **McDuffie HH**, Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA. Clustering of cancer among families of cases with Hodgkin Lymphoma (HL), Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Soft Tissue Sarcoma (STS) and control subjects. *BMC Cancer* 2009; **9**: 70

16 **Mensah FK**, Willett EV, Ansell P, Adamson PJ, Roman E. Non-Hodgkin's lymphoma and family history of hematologic malignancy. *Am J Epidemiol* 2007; **165**: 126-133

17 **Negri E**, Talamini R, Montella M, Dal Maso L, Crispo A, Spina M, La Vecchia C, Franceschi S. Family history of hemolymphopoietic and other cancers and risk of non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 245-250

18 **Wang SS**, Slager SL, Brennan P, Holly EA, De Sanjose S, Bernstein L, Boffetta P, Cerhan JR, Maynadie M, Spinelli JJ, Chiu BC, Cocco PL, Mensah F, Zhang Y, Nieters A, Dal Maso L, Bracci PM, Costantini AS, Vineis P, Severson RK, Roman E, Cozen W, Weisenburger D, Davis S, Franceschi S, La Vecchia C, Foretova L, Becker N, Staines A, Vornanen M, Zheng T, Hartge P. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007; **109**: 3479-3488

19 **Zhu K**, Levine RS, Gu Y, Brann EA, Hall I, Caplan LS, Baum MK. Non-Hodgkin's lymphoma and family history of malignant tumors in a case-control study (United States). *Cancer Causes Control* 1998; **9**: 77-82

20 **Troch M**, Woehrer S, Streubel B, Weissel M, Hoffmann M, Müllauer L, Chott A, Raderer M. Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) in patients with MALT lymphoma. *Ann Oncol* 2008; **19**: 1336-1339

21 **Fischbach W**, Goebeler ME, Ruskone-Fourmestraux A, Wündisch T, Neubauer A, Raderer M, Savio A. Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of Helicobacter pylori can be managed safely by a watch and wait strategy: experience from a large international series. *Gut* 2007; **56**: 1685-1687

22 **Ruskoné-Fourmestraux A**, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, Montalban C, Raderer M, Savio A, Wotherspoon A. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut* 2011; **60**: 747-758

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM