*Case study*

# Synchronous thyroid and gastric mantle cell lymphoma.

**Running title: thyroid and gastric mantle cell lymphoma.**


**Abstract:**

Introduction:

Mantle cell lymphoma (MCL) is a distinct entity within the World Health Organization classification of lymphoid neoplasm1 and represents approximately 8% of lymphoma. Patients with mantle-cell lymphoma typically present with extensive disease and involvement of multiple lymph nodes as well as the spleen, bone marrow, blood, and gastrointestinal tract. MCL occurs exceptionally. The MCL of the stomach is also an exceptional occurrence.

Observation: we describe the case of a 58-year-old male who was diagnosed with thyroid and gastric MCL. The patient was classified into high risk group according to the Mantle Cell Lymphoma International Prognostic Index (MIPI). The R-CHOP (Rituximab, Cyclophosphamide, Adriablastine, Vincristine and Prednisone) regimen was started and complete remission was achieved after 8 courses. He currently receives a maintenance treatment with rituximab every two months.

Conclusion: This case is a combination of two rather infrequent extranodal localizations of the MCL.



**Keywords:** Mantle cell lymphoma- thyroid- stomach- chemotherapy.


## Introduction:

Thyroid non-Hodgkin's lymphoma (TNHL) represents 2-8% of thyroid malignancies and 1-2% of extranodal lymphomas [1]. Diffuse large B cell lymphoma is the most common histological type, accounting for up to 70% of primary TNHL [2]. The mucosa-associated lymphoid tissue lymphoma (MALT) accounts for 15-40% of primary TNHL [2]. Follicular lymphoma of the thyroid is very rare. Mantle cell lymphoma of the thyroid (MCL) occurs exceptionally. In the gastrointestinal tract, the MALT is the most common low-grade lymphoma, arising mainly in the stomach (60%-70%) [3]. The MCL of the stomach is also an exceptional occurrence. To our knowledge, this is the first report of a patient with synchronous thyroid and gastric MCL.

## Case report:

A 58-year-old male was admitted in the department of ENT for further evaluation of a mass of the thyroid gland, associated with gradually increased pain and dyspnea. He had no family or personnel history for thyroid pathology and gastric complaints. The local examination of the thyroid revealed a painless palpable mass which was hard in consistency, fixed to the musculature and invading the entire thyroid (Figure 1). The ECOG Performance Status was equal to 2. The rest of the physical examination was normal (no palpable lymph nodes and no hepatosplenomegaly). Serum laboratory values, including LDH, b2-microglobulin, fT4 and

TSH were within normal ranges. Anti-TSH receptor antibodies were absent. Viral serology and particularly HIV, HBV, HCV and EBV tests were negative. Complete blood cell count was normal. Ultrasound revealed a heterogeneous nodule involving almost the entire lobe of the thyroid. The thyroid fine needle aspiration was not performed. After a biopsy of the thyroid mass, histological examination demonstrated a diffuse lymphomatous infiltrate. Lymphoepithelial lesions were characterized by neoplastic lymphocytes that infiltrated and destroyed thyroid follicles, often showing regressive changes. Lymphoma cells appeared monotonous and slightly larger than small lymphocytes. Their nuclei displayed variable degrees of angulation with fairly condensed chromatin and their cytoplasm was very scanty (Figure 2A). Immunohistochemically, the tumor cells were positive for CD20, cyclin D1 and CD5 (Figure 2(B, C, D)) and negative for CD23, CD10, and the epithelial membrane antigen. Few CD3 positive lymphoid cells were detected. Ki 67 was identified in 80% of neoplastic cells. In consequence of this finding, the tumor was diagnosed as MCL. The examination of the ENT was normal. Computed tomography scans showed cervical lymph node associated with two nodular thickening at the cardia and fundus regions of the gastric wall. The gastroscopy showed a loss of substance of 15 mm in diameter at the gastric antrum whose biopsy revealed the infiltration of the gastric mucosa by the same lymphoid cell proliferation (Figure 2E). The cells were also positive for CD20, CD5 and cyclin D1 and negative for CD10. Ki 67 was identified in 75% of neoplastic cells. Helicobacter pylori infection was not detected. In consequence of this finding, the diagnosis of gastric MCL was confirmed. The colonoscopy was not performed. The bone marrow biopsy revealed the absence of a medullary extension of the lymphoma. Cytogenetic study of the bone marrow cells was normal. Cytogenetic analysis was not performed on the fragments of the thyroid and gastric biopsy. The final diagnosis was a double gastric and thyroid localization of MCL. After this staging, lymphoma is classified as stage IV according to the classification of Ann Arbor. The patient was classified into high risk group according to the Mantle Cell Lymphoma International Prognostic Index (MIPI). The R-CHOP (Rituximab, Cyclophosphamide, Adriablastine, Vincristine and Prednisone) regimen was started and complete remission was achieved after 8 courses. Control gastroscopy showed a cicatricial ulcer of the antrum whose biopsy was negative. Our patient was not eligible for autologous stem cell transplantation (ASCT) consolidation because of his average performance status. He currently receives a maintenance treatment with rituximab every two months. Rituximab maintenance therapy will be applied for 2 years. No relapse has occurred during a follow-up of 4 months.

**Discussion:**

MCL is an aggressive lymphoma of older adults, with a male preponderance and it represents 6% of all NHL [4] and just a minority of the extra nodal lymphomas [5]. Clonal plasma cell differentiation may occur within germinal center in some cases of MCL [6]. Patients with extra nodal MCL will be found, in the most of cases, to have lymphadenopathy or more widespread disease on staging [5]. Lymphoproliferative disorders affecting the thyroid are characterized by diverse clinical and pathologic spectrum and must be differentiated from carcinoma and benign thyroiditis. MCL of the thyroid is an exceptional occurrence. The clinical presentations include an enlarging neck mass, as in our case, but patients may also present the symptoms of dysphagia, hoarseness and choking, or a cold thyroid nodule [7]. Since MCL of the thyroid is an uncommon malignancy, a misdiagnosis is possible. Other malignant thyroid tumors, especially anaplastic carcinoma, and other lymphomas, such as follicular lymphoma and marginal zone lymphoma must be differentiated from MCL because of the subsequent management strategies. In such cases, diagnosis and subclassification can be established using study of routine sections augmented by immunohistochemistry [8].

Despite the absence of digestive clinical symptoms in our case, the gastroscopy showed a gastric infiltration by the MCL. In other cases, patients may have diarrhea and abdominal pain [9]. By using additional immunological and molecular markers, lymphomas are classified into subtypes according to the World Health Organization classification and that is important for further decision making. For an adequate prognostic evaluation and appropriate clinical decisions, histological diagnosis must be combined with IPI prognostic parameters. The MCL international prognostic index has been proposed as a new prognostic index for MCL. It considers age, performance status, LDH level and leukocyte count as prognostic factors [10]. In MCL, gastrointestinal tract involvement has not been identified so far as an adverse prognostic factor [11]. Our patient presents with synchronous thyroid and gastric MCL justifying systemic treatment with chemo immunotherapy. The poorest 5-year survival of all the non-Hodgkin's lymphoma subtypes in the NHL classification project was observed with MCL and it is considered to be incurable with standard therapies [12]. CHOP plus rituximab (R) is associated with high response rates but the progression-free survival (PFS) is disappointingly short (median 16–20 months) [13, 14, 15]. A benefit for selected patients using autologous stem cell transplantation (ASCT) consolidation in first remission has been suggested in some phase II studies and registry studies [16–17]. However, many patients are not eligible for autograft and randomized clinical trial did not demonstrate the prolongation in overall survival with this strategy [18]. A better outcome with a regimen consisting of R-hyper CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone plus rituximab) alternating with rituximab plus methotrexate and cytarabine (R-Mtx/AraC) has been reported [19]. But, this regimen can be toxic for patients over the age of 65 and younger patients with co-morbid illness. Since the median age for newly diagnosed mantle cell lymphoma patients is 64, approaches that do not include stem cell transplantation or involve highly aggressive chemotherapy regimens need to be developed. Two large studies show a better PFS for untreated MCL by the application of maintenance rituximab for 2 years following the completion of a moderately aggressive chemo immunotherapy regimen [20-21]. Our patient had an excellent response with R-CHOP, although this regimen is no more considered the first line therapy in MCL. It was demonstrated that induction with rituximab and cytarabine-based regimens [22] and the addition of lenalidomide to rituximab-bendamustine (R-B) [23] as first-line treatment to elderly MCL patients were associated with a high rate of CR and molecular remission. In our case, a further follow up is necessary to detect a relapse.

In conclusion, the double localization (thyroid and gastric) and the histological type MCL of the lesion make our patient's case really remarkable.

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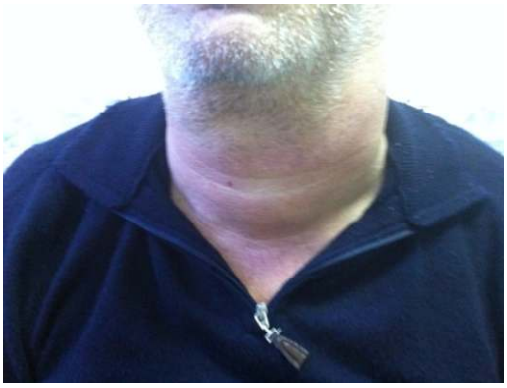


**Figure 1:** The mass of the thyroid gland.

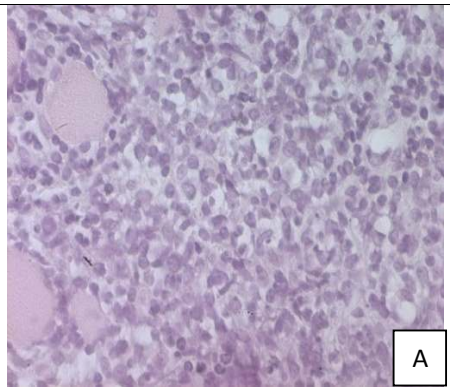
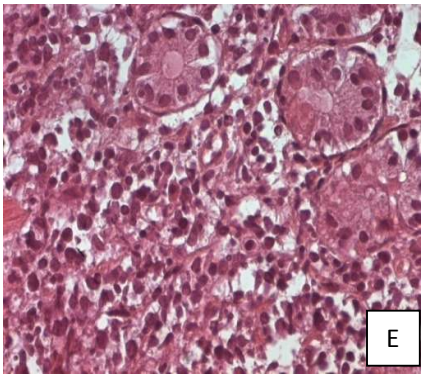
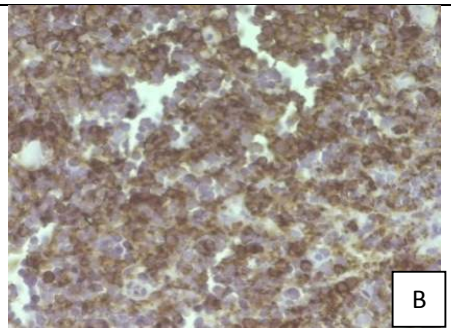
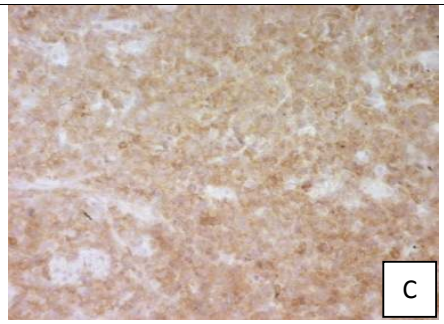
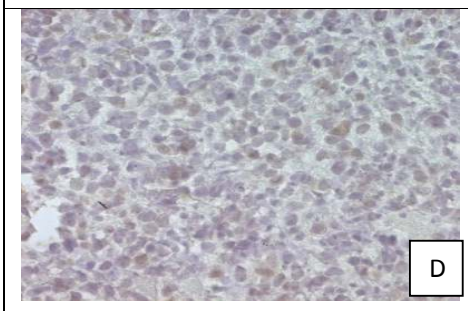
| Thyroid | Stomach |
| --- | --- |
|   |   |
|   | |
|   | |
|   | |

**Figure 2**: (A)-Extensive lymphoid infiltrate destroys the thyroid tissue (hematoxylin–eosin, 400X).

(B)- The tumor cells were positive for CD20

(C)- The tumor cells were positive for CD5

(D) - The tumor cells were positive for cyclin D1 antigen

(E)- The infiltration of the gastric mucosa by the same lymphoid cell proliferation (hematoxylin–eosin, 400X).