



Unusual transformation of primary extranodal marginal zone B cell lymphoma of the uterus into a nodal follicular lymphoma grade IIIB

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Dear Editor,

According to the WHO classification of non-Hodgkin lymphoma, extranodal marginal zone B cell lymphomas of mucosa-associated lymphatic tissue (MALT) is defined as a group of NHL (non-Hodgkin lymphoma) that account for approximately 7–8% of all B cell lymphomas [1]. The most common location of MALT is the gastrointestinal tract. A manifestation of the uterus is a rarity and to our best knowledge, fewer than 20 case reports of marginal zone B cell lymphoma of the uterus have been reported so far in literature [2, 3].

The histological transformation into an aggressive lymphoma occurs in approximately 4% and is associated with an inferior treatment outcome [4]. MALT lymphoma is characterized by recurrent chromosomal translocations, leading to the activation of the NF- κ B signaling pathway.

In 2011, a 60-year-old woman presented to our outpatient department with an extranodal marginal zone B cell lymphoma of the uterus. Morphologic examination of the specimen showed epithelium, which was partly invaded and destroyed by discrete aggregates of small lymphoma cells resulting in the so-called lymphoepithelial lesions. Tumor cells were CD20+, CD43+, and IgM+ and negative for CD5, CD10, CD23, and Cyclin D1 (Fig. 1b–d).

An external staging CT scan revealed no other extranodal or nodal manifestation as examination of the bone marrow biopsy specimen showed no lymphoma infiltration.

The lymphoma was classified as stage I according to the Ann Arbor classification. In the interdisciplinary tumor board, hysterectomy was recommended for a localized MALT lymphoma with a potential curative option.

Two weeks after hysterectomy, a PET/CT scan showed a suspicious metabolic uptake in thoracic, axillary, and abdominal lymph nodes (Fig. 1a). Therefore, PET-CT led to an upstaging to stage III. Because the patient presented with asymptomatic disease, a watch and wait strategy was recommended.

At the beginning of 2017, the patient presented with a disease progression with multifocal involvement of the liver, suspected manifestation of the spleen and both kidneys (Fig. 1e). A nodal biopsy of an inguinal lymph node of the left side was performed. The histology of the needle biopsy revealed a lymphoma, predominantly consisting of sheets of centroblasts with a follicular growth pattern. Immunohistochemically, the lymphoma was positive for CD19, CD20, and CD10. The proliferation rate (Ki67) was high with 60% (Fig. 1f–h); due to the follicular growth pattern and the immunohistological profile, a grade IIIB follicular lymphoma was diagnosed. Using consensus primers for the variable and joining segments of the Ig heavy chain (IgH), the resulting IgH gene rearrangement was identical for FR1, FR2, and FR3 in the lymphoma of the uterus and in the lymph node, proving a clonal relationship between the lymphomas.

Correspondingly, a significantly increased LDH was found in the laboratory workup. Due to the transformation into a high-grade follicular lymphoma, the patient was included in a therapy study for aggressive B cell lymphomas (Optimal trial, NCT01478542). After 12 cycles of rituximab and 6 cycles of CHLIP-14 (cyclophosphamide, doxorubicin, liposomal vincristine, and prednisone), complete remission was achieved. At this time, the patient is in complete remission.

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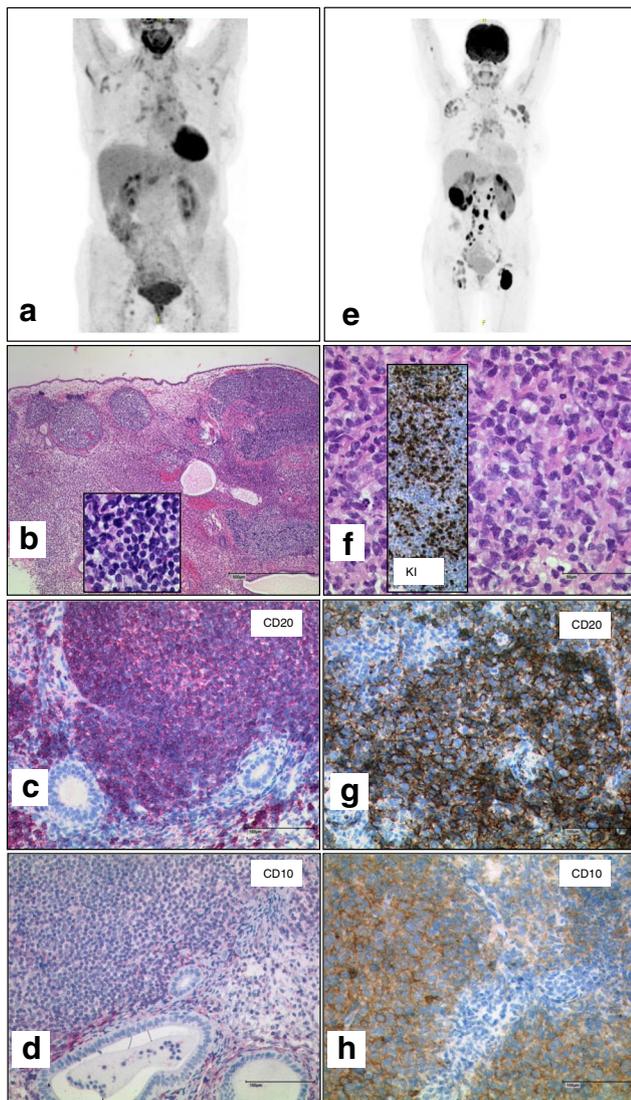


Fig. 1 **a** PET/CT after hysterectomy in 2011: Some clearly marked FDG-positive nodes on the right cervical, left nuchal, paratracheal, infracarinal, and bilateral hilar and axillary lymph nodes are seen (SUV max. up to 4, SUV mean up to 3.6). Strong FDG accumulating lymph nodes (SUV max. up to 3.7, SUV mean up to 3.4) up to 28 × 13 mm in size around the hepatic artery and the vena portae. **b** Hematoxylin and eosin staining of the uterus shows a lymphoma with a marginal zone-like growth pattern forming larger confluent areas: The centrocytic-like lymphoma cells (insert) infiltrate the epithelium of the mucosa of the uterus and colonize preexisting follicles. **c** The lymphoma is strongly CD20-positive and CD10-negative (**d**). **e** PET/CT at the time of transformation in 2017: significant progress with moderate to partly very intense metabolism-enhanced lymph node manifestations are noted. The largest most intensified metabolic and most progressive lesions are found on the left inguinal, abdominal, and axillary lymph nodes. The scan shows pluritopic organ involvement with multifocal involvement of the liver, manifestation of both kidneys, and suspected involvement of the spleen. **f** The lymphoma consists of sheets of centroblasts and has a high Ki-67 index (insert). **g** In a CD20 staining, the lymphoma has a vaguely follicular growth pattern and is CD10-positive (**h**)

We performed an interphase FISH study on our paraffin-embedded specimen from the marginal zone lymphoma of the uterus. We did not find any of the known recurrent chromosomal

translocations in MALT (negative FISH for t(11;18), t(1;14), t(14;18), t(3;14)). This is in line with the sparse data, which already exist [2]. Interestingly, we could detect trisomy 3 in 36% of the cells by FISH in the MALT lymphoma of the uterus. However, after transformation into the high-grade lymphoma, trisomy 3 was no longer detectable. This finding may indicate that the transformation occurred in a common malignant stem cell in which the trisomy was not present yet, that the trisomy 3 was acquired by a subclone later on, and that transformation into the grade IIIB follicular lymphoma occurred in a trisomy 3-negative lymphoma subpopulation.

If a transformation occurs, a diffuse large cell lymphoma, a Hodgkin's lymphoma, or Burkitt's lymphoma is described [5]. A transformation in a follicular lymphoma, as presented in this study, has not been described so far.

From a clinical point of view, this case is relevant regarding the staging procedure.

According to current international guidelines, routine use of PET-CT in MALT is not recommended and still controversial [6]. According to a meta-analysis, 71% of patients with marginal zone lymphoma are FDG-positive in PET-CT [7]. The presented case raises the question whether a PET-CT should be performed routinely in potentially curative patients with MALT.

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Compliance with ethical standards

Ethical standards and patient informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the patient for being included in the study.

Conflicts of interest The authors declare that they have no conflict of interest.

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References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 127(20):2375–2390. <https://doi.org/10.1182/blood-2016-01-643569>
2. Takimoto T, Maegawa S, Tatsumi H, Nagoshi H, Chinen Y, Shimura Y, Kobayashi T, Horiike S, Nakamura S, Kitawaki J, Kuroda J, Taniwaki M (2017) Extranodal marginal zone lymphoma of the uterine cervix with concomitant copy number gains of the MALT1 and BCL2 genes: a case report. *Oncol Lett* 13(5):3641–3645. <https://doi.org/10.3892/ol.2017.5944>
3. Magnoli F, Cimetti L, Bernasconi B, Sahnane N, Redaelli I, Riva C, Uccella S (2016) Primary extranodal marginal cell lymphoma, MALT type, of the endometrium arising in a patient with rheumatoid

- arthritis: report of a case. *Int J Gynecol Pathol* 35(4):327–332. <https://doi.org/10.1097/PGP.0000000000000244>
4. Casulo C, Friedberg J (2017) Transformation of marginal zone lymphoma (and association with other lymphomas). *Best Pract Res Clin Haematol* 30(1–2):131–138. <https://doi.org/10.1016/j.beha.2016.08.029>
 5. Conconi A, Franceschetti S, Aprile von Hohenstaufen K, Margiotta-Casaluci G, Stathis A, Moccia AA, Bertoni F, Ramponi A, Mazzucchelli L, Cavalli F, Gaidano G, Zucca E (2015) Histologic transformation in marginal zone lymphomas. *Ann Oncol* 26(11):2329–2335. <https://doi.org/10.1093/annonc/mdv368>
 6. Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, Kluin-Nelemans JC, Ladetto M, Le Gouill S, Iannitto E, Pileri S, Rodriguez J, Schmitz N, Wotherspoon A, Zinzani P, Zucca E (2013) ESMO consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol* 24(4):857–877. <https://doi.org/10.1093/annonc/mds643>
 7. Treglia G, Zucca E, Sadeghi R, Cavalli F, Giovanella L, Ceriani L (2015) Detection rate of fluorine-18-fluorodeoxyglucose positron emission tomography in patients with marginal zone lymphoma of MALT type: a meta-analysis. *Hematol Oncol* 33(3):113–124. <https://doi.org/10.1002/hon.2152>