Subcutaneous dissemination pattern in extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma

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ABSTRACT

Background
Mucosa-associated lymphoid tissue (MALT) lymphoma is among the most common forms of extranodal lymphomas, but little is known about subcutaneous involvement in patients with non-primary cutaneous marginal zone lymphomas.

Design and Methods
Patients with MALT lymphoma diagnosed and treated at our institution between 1999 and 2010 were analyzed for subcutaneous deposits from MALT lymphoma diagnosed in another organ. Histological, clinical and genetic findings were assessed.

Results
Among 216 patients with MALT lymphoma, 12 had subcutaneous deposits from MALT lymphoma (5.5%). In two patients, these lesions were present at diagnosis, while they constituted the site of relapse at an interval between 5 to 144 months in the remaining cases. Interestingly, nine of the 12 patients with subcutaneous deposits had originally been diagnosed with MALT lymphoma of the ocular adnexa (total number=51; 20%), and the other three had MALT lymphoma in the breast (total number=5; 60%). None of the patients with gastric (n=86), salivary gland (n=32) or pulmonary (n=19) MALT lymphomas had subcutaneous involvement during a median follow-up time of 87 months (range; 4 to 119 months).

Conclusions
Our data show that subcutaneous MALT lymphoma involvement is a rare event in patients with prior non-cutaneous extranodal marginal zone lymphoma. However, it seems to be almost exclusively associated with MALT lymphoma of the ocular adnexa and the breast, suggesting as yet undefined interactions between potentially embryonically related organ systems.

Key words: MALT lymphoma, ocular adnexa, cutaneous lymphoma.

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Introduction

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is a relatively common disease, which has become the paradigm for an infection-driven lymphoma. Accounting for roughly 7% of all newly diagnosed lymphomas, it is mainly found in the stomach where it is associated with *Helicobacter pylori* infection in the large majority of patients.[1,2] In view of this finding, antibiotic treatment targeting *H. pylori* has been applied in patients with early stage gastric MALT lymphoma, and has become standard treatment for this population of patients due to the impressive results in terms of lymphoma response[3-6] It is currently estimated that about 75% of patients with *H. pylori*-associated early stage gastric MALT lymphoma will respond to antibiotic therapy alone. Risk factors for non-response include the presence of the MALT lymphoma-specific t(11;18)(q21;q21) translocation as well as the presence of an autoimmune disease, which seems to be more common in gastric lymphomas than initially suspected.[7,8]

Apart from the stomach, which constitutes the site of origin in about 50% of patients, MALT lymphoma may be diagnosed in almost every organ of the human body with a predominance in the salivary glands, the ocular adnexa and the lung.[1] Besides the ocular adnexa, where an infectious background has been hypothesized with *Chlamydia psittaci* as a potential source of antigenic drive,[9-11] autoimmune diseases such as Sjögren's syndrome or chronic autoimmune (Hashimoto's) thyroiditis have emerged as a major pathogenic background for lymphoma development.[1] There are clinical differences in terms of dissemination between gastric and non-gastric MALT lymphomas, as the rate of multiorgan involvement has been reported to be almost 50% in non-gastric MALT lymphomas, compared to 25% in gastric MALT lymphomas.[12]

Apart from the gastrointestinal tract, the skin is among the most prominent organs giving rise to extranodal lymphomas. These neoplasms are, however, predominantly of T-cell origin, with mycosis fungoides being the most commonly encountered entity.[13] In contrast, primary cutaneous B-cell lymphomas are relatively rare, and account for only 20% of cutaneous lymphomas. Cutaneous marginal zone B-cell lymphoma has been described in analogy to MALT-lymphoma, and a few reports have suggested a potential association with Borrelia infection.[14] While cutaneous marginal zone B-cell lymphoma is characterized by a propensity to repeated relapses, these recurrences are located exclusively in the skin without spread to other organs, in contrast to organ-derived MALT lymphomas.

Interestingly, little is known about subcutaneous involvement in patients with gastric and non-gastric MALT lymphomas, although two Italian studies found that extranodal marginal zone lymphomas involving the subcutaneous tissue were related to infection with hepatitis C virus (HCV).[15,16] In view of this, we conducted a retrospective analysis of all patients with MALT lymphoma diagnosed, staged, treated and followed at our institution between 1999 and 2010 in order to assess the propensity for subcutaneous spread.

Design and Methods

All patients diagnosed with and treated for histologically verified MALT lymphoma at our institution between 1999 and 2010 were retrospectively analyzed in this study which was approved by the Ethical Board of the University of Vienna. For patients who had been referred for recurrent MALT lymphoma during this period, initial histological information was obtained and re-assessed as was any medical history outside our department. Only patients with a definitive histological diagnosis according to the criteria outlined in the recent World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissue[1] with histological material available at our institution were included in the analysis.

All patients had undergone staging including at least computed tomography of the thorax and abdomen, gastroscopy, and imaging of the orbit and salivary glands. Patients whose MALT lymphoma was of gastric origin also underwent at least one endosonography of the upper gastrointestinal tract and colonoscopy. A bone marrow biopsy had been performed in the initial 140 patients, but was abandoned as a routine procedure due to the low rate of bone marrow involvement, i.e. <2%.[12] A routine dermatological check-up had not been part of the staging in any of the patients.

The patients' charts as well as all imaging reports available were re-assessed for information on subcutaneous deposits. For patients with evidence of subcutaneous spread of MALT lymphoma, histological samples were again evaluated to verify the presence of MALT lymphoma. Information abstracted from patients' records included the presence or absence of subcutaneous deposits at diagnosis, location of the primary lymphoma, time from initial diagnosis of MALT lymphoma to subcutaneous dissemination, nature of subcutaneous deposits (i.e. single or multiple) and their localization, the patient's clinical course and survival. In addition, the presence/absence of an autoimmune disease (which was routinely assessed in all patients since 1999) as well as hepatitis A, B, and C was determined.

Results

Overall, 216 patients with MALT lymphoma diagnosed and treated at our institution were identified. Follow-up data for a median duration of 87 months (range, 4 to 289 months) were available. The large majority of patients had gastric MALT lymphoma (n= 86), 51 patients were diagnosed with MALT lymphoma of the ocular adnexa (12 conjunctival, 27 of the orbit and 12 in the lacrimal gland), 32 of the salivary glands (28 parotid and 4 submandibular), 19 of the lung, 7 of the thyroid, 6 of the small intestine and 5 patients each had MALT lymphoma of the breast and the liver.

In total, 12 out of 216 patients (5.5%) were diagnosed with clinically apparent and subsequently histologically verified MALT lymphoma involvement of subcutaneous tissue (for detailed information, see Table 1). These lesions were identified on routine computed tomography scans in ten patients, while two patients complained of clinically obvious lesions. In all patients, these lymphoma manifestations exclusively involved subcutaneous tissue without affecting the epidermal layer. Furthermore, no involvement of glandular structures was found, lymphoepithelial lesions were absent, and none of the patients showed evidence of plasmacytic differentiation. Otherwise, the lymphoma infiltrations were microscopically and immunohistochemically rated as MALT lymphomas according to the recent WHO classification[1] without any features distinctive from MALT lymphomas in other sites. Ten patients

Table 1. Patients' characteristics.

Gender /age	Initial localization of MALT	Treatment of Initial MALT	Time to subcutaneous manifestation	Method of detection subcutaneous manifestation	Detection method of subcutaneous manifestation	Treatment of subcutaneous manifestation	Status from initial diagnosis
Female/54	breast	oxaliplatin	31 months	cervical	CT[1]	excision, watchful waiting	lost to follow up at 50 months
Female/ 58	orbit	radiation	49 months	gluteal	CT	bortezomib	alive at 2004 months
Female/61	orbit	radiation	119 months	suprapubic	CT	CHOP[2]	alive at 244 months
Female/64	conjunctiva	excision	43 months	lower back	CT	R-CHOP[3]	alive at 195 months
Female/59	breast	rituximab	11 months	chest wall (contralateral, mutiple)	CT	watchful waiting	alive at 24 months
Female/49	orbit	radiation	synchronous, detected during staging	gluteal	PET-CT	radiation	alive at 8 months
Female/77	lacrimal gland	radiation	63 months and 122 months	periumbilical paravertebral/ lower back	CT PET-CT	R-CNOP[4] watchful waiting	dead (heart disease) at 137 months
Female/70	breast	oxaliplatin	synchronous, detected during staging 28 months	chest wall (contralateral) gluteal (multiple)	CT self-assessment	R-CHOP	alive at 98 months
Female/71	orbit	COP	26 months	forearm	self-assessment	R-CHOP	alive at 93 months
Male/84	orbit, cervical LN	radiation, MCP	16 months	occipital	CT	radiation	dead (MCI) at 26 months
Male/80	lacrimal gland	radiation	5 months	face	self-assessment	COP[5]	dead (heart disease) at 11 months
Female /85	conjunctiva	radiation	41 months	lower back	CT	watchful waiting	dead (senility) at 49 months

[1]CT: computed tomography, [2]CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone, [3]R-CHOP: rituximab plus CHOP, [4]R-CNOP: rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisolone, [5]COP: cyclophosphamide, vincristine, prednisolone. LN: lymph nodes; MCI: myocardial infarct.

had single subcutaneous lesions, while two patients had two and four deposits, measuring in size between 1.5 and 7.5 cm. The deposits were located predominantly in the lower back/gluteal region (4 patients) and chest wall (3 patients), while one patient each had cervical, facial, occipital, elbow and suprapubic deposits. A lesion in the lower back in one individual was initially considered as a granuloma following an intramuscular injection, but was biopsied after progression was detected by computed tomography follow-up. There was no documented history of trauma or inflammation among the remaining patients. Two patients developed another subcutaneous relapse 38 and 59 months after successful therapy of the initial deposits (Table 1). Interestingly, no other organ manifestations were found in any of the patients during clinical check-ups following diagnosis of subcutaneous manifestations.

Out of the 12 patients with subcutaneous deposits of MALT lymphoma, only two were male and the remaining ten were female. Two patients were diagnosed with subcutaneous deposits during initial staging for orbital lymphoma, while subcutaneous involvement represented a site of relapse in ten patients. The primary site of MALT lymphoma was the ocular adnexa in nine cases and the breast in the other three cases; no patients with other localizations of lymphoma developed subcutaneous disease during follow-up. The median time between initial diagnosis and subcutaneous relapse was 31 months (range, 5 to 122 months). Eight of the 12 patients had underlying autoimmune diseases: three patients had Sjögren's syndrome, two patients each presented with rheumatoid arthritis and chronic autoimmune (Hashimoto's) thyroiditis, while one patient suffered from ankylosing spondylitis. In ten patients in whom the subcutaneous deposit was a manifestation of relapsed MALT lymphoma, the subcutaneous lesion was the first site of relapse, while two patients had secondary organ relapses before another subcutaneous relapse (following recurrence in the breast and the lung in one patient each).

Serological studies for *H. pylori* were negative in nine out of 11 patients assessed and positive in two; no evidence of infection with Borrelia was found in ten patients investigated serologically. Laboratory tests for hepatitis A, B, and C were performed in all 12 patients and showed that 11 patients were negative for hepatitis. One patient was found to be an HBV carrier, as demonstrated by positivity for Hbs-antigen, but had no signs of impaired hepatic function.

After a median follow up of 50 months (range, 8 to 244 months) for all 12 patients, eight patients are alive, while three patients have died due to cardiac events and one of old age. One patient was lost to follow-up 50 months after the initial diagnosis.

Genetic data were available for seven of the 12 patients.

Four patients had numerical aberrations, with trisomy 18 being present in all cases, and one patient had an additional trisomy 3. None of the patients investigated had evidence of t(11;18)(q21;q21) or t(14;18) *IGH/MALT* translocations.

Discussion

MALT lymphoma is a B-cell malignancy with a marked propensity for homing to extranodal organs. This propensity is thought to be mediated by mucosal structures such as $\alpha_4\beta_7$ integrins and their respective interaction with endothelial venules and explains the preferential mucosal dissemination of MALT lymphomas.[17,18] Investigations of dissemination and relapse patterns have shown a higher risk of multiorgan involvement as well as relapse in patients initially diagnosed with non-gastric MALT-lymphoma.[12]

To our knowledge, this is the largest series in which the characteristics of secondary subcutaneous MALT lymphoma have been investigated, albeit in a retrospective way. Judging from our data, subcutaneous spread from MALT-lymphoma is exceedingly rare, as it occurred in only 12 out of 216 patients (5.5%) seen at our institution between 1999 and 2010. Interestingly, the subcutis was the only site involved in all 12 patients diagnosed, and the outcome was generally good in these patients. While the caveats of a retrospective series apply to our data, some interesting features have emerged.

One of the most striking findings was that the phenomenon of subcutaneous MALT lymphoma represented secondary tissue involvement without affecting the epidermal layer. In contrast to the situation with primary cutaneous marginal zone B-cell lymphoma, subcutaneous deposits in all 12 patients were either diagnosed on routine computed tomography which led to a subsequent, confirmatory biopsy, or became apparent by self-assessment. As skin status was not part of our staging routine, none of the subcutaneous sites was found during a first-line dermatological evaluation.

The most interesting finding in our series was, however, the fact that nine out of the 12 patients had initially been diagnosed with MALT lymphoma of the ocular adnexa, and the other three with MALT lymphoma of the breast. In contrast, no patients with gastrointestinal MALT lymphoma (including 86 cases of gastric MALT lymphoma) or MALT lymphoma in salivary glands, lungs or any other site were observed to have spread to subcutaneous tissue. We cannot, at present, explain this finding. However, it is tempting to speculate that the ocular adnexa, breast and subcutaneous tissue might be immunologically linked to a certain extent. Lymphocytes generated within a MALT environment show homing behavior to mucosal structures, as repeatedly reported.[19] In fact, further specialization of immunological trafficking in terms of gastro-intestinal *versus* non-gastrointestinal mucosal homing has been documented theoretically[19] as well as clinically.[12] However, in the model proposed by Brandtzaeg *et al.*, priming of B cells in tonsils, Eustachian tube and bronchial MALT was suggested to lead to circulation to orbital, nasal and salivary glands, but also bronchus-associated lymphoid tissue. Mammary glands were suggested to be "effector organs" of lymphocyte homing from both primary sites already mentioned, as well as from the intestinal MALT system.[19]

In this model no crosstalk with subcutaneous tissue was proposed. In fact the mechanism of existence of subcutaneous MALT in deficiency of mucosal structures is puzzling. No evidence of localized trauma or inflammation was detected in our patients, and no infectious sources were consistently identified in this series. No signs of exposure to Borrelia were recognized in these 12 patients, and only one patient was positive for hepatitis B virus/Hbs antigen. To a certain extent, these data are in line with Italian reports of a spread of orbital MALT lymphoma to the subcutaneous tissue. However, it is not clear whether the lymphomas in one of those reports, which described seven indolent orbital lymphomas in 1985, would be classified as MALT lymphomas according to current criteria.[20] The other publication was based exclusively on data generated in patients who were positive for HCV.[15] Primary subcutaneous marginal zone lymphoma was described as an HCV-associated disease by Paulli and co-workers.[16] None of our patients tested positive for HCV, suggesting that the phenomenon of subcutaneous spread following ocular adnexal lymphoma might not be triggered solely by HCV. Interestingly, eight out of our 12 patients (66%) had an underlying autoimmune disease; in a previous study including 158 Austrian patients with MALT lymphoma, 39% (i.e. 61/158 patients) were found to be positive for an underlying autoimmune disease.[7] However, given the small number of patients, this information should be interpreted with caution. Nevertheless, the high frequency of autoimmune diseases in our small series suggests a potential, as yet unrecognized, association with subcutaneous spread.

According to our clinical data, a specific homing pattern from the ocular adnexa and breast to the subcutis is likely, albeit in a small number of patients. In view of this, we hypothesize that the preferential circulation between ocular adnexa and subcutis as well as breast and subcutaneous tissue, respectively, might be determined by the shared origin of these organs/tissues due to (human) embryonic development. Although it remains hypothetical for the moment, the common ectodermal derivation of lacrimal gland/orbital structures, breast and subcutaneous structures as opposed to the entodermal source of salivary glands, gastrointestinal tract and lung might explain the pattern observed in our patients. Actually, the development of lymphoid tissues following fetal developmental pathways has already been suggested for mucosal lymphoid tissue in the adult gut.[21] In addition, it has been demonstrated that lymphoid stromal cells programmed during ontogeny might lead to lymphoid accumulation in adult life.[22] The molecular mechanisms should be addressed in further investigations to elucidate the processes operative in this putative immunological link.

In terms of clinical applications, our data suggest that routine dermatological assessment might not be necessary in the large majority of patients with MALT lymphoma, but should be performed routinely in patients with MALT lymphoma of the ocular adnexa and the breast. The outcome of this small series of patients was generally good, and did not suggest that subcutaneous dissemination has an unfavorable clinical impact.

Authorship and Disclosures

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