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MALT lymphoma associated genetic aberrations occur at different frequencies in primary and secondary intestinal MALT lymphomas

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Background and aims: Limited data are available on intestinal MALT lymphoma owing to its relatively rare occurrence. The frequency of associated genetic changes was therefore analysed in intestinal MALT lymphoma to determine whether primary and secondary examples may be distinguished by their genetic profile.

Methods: Patients diagnosed with MALT lymphoma involving the intestine were evaluated and compared with 71 cases with localised gastric MALT lymphoma. Paraffin embedded samples were evaluated for t(11;18)(q21;q21) by reverse transcription polymerase chain reaction, and by fluorescence in situ hybridisation for t(14;18)(q32;q21), t(1;14)(p22;q32), and trisomies 3 and 18.

Results: 30 consecutive patients with MALT lymphoma involving the intestine were identified: 16 had primary intestinal lymphoma and 14 had secondary MALT lymphoma. t(11;18)(q21;q21) was found in one third of the patients, but there was a significant difference between the secondary MALT lymphomas and the primary intestinal and gastric MALT lymphoma groups (57% v 12.5%, $p=0.019$, and 57% v 24%, $p=0.022$). Two patients with primary intestinal MALT lymphomas were positive for t(1;14)(p22;q32) and none was positive for t(14;18)(q32;q21). Primary intestinal MALT lymphoma had a significantly higher frequency of trisomies 3 or 18 (81% v 36%, $p=0.024$; 81% v 14%, $p<0.001$), in contrast to secondary intestinal MALT lymphomas and localised gastric MALT lymphomas.

Conclusions: The genetic profile of primary intestinal MALT lymphomas appears to be different from that of secondary intestinal or local gastric MALT lymphomas. Because of the high prevalence of trisomy 3 or 18, or both, in primary intestinal lymphoma, these numerical aberrations might be regarded as a genetic hallmark of the disease.

Extranodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma) is listed as a distinct clinicopathological entity in the WHO classification of malignant lymphomas.¹ The majority of MALT lymphomas occur in the stomach, but this type of lymphoma may affect virtually every organ in the human body, including the ocular adnexa and orbit, lung, salivary glands, thyroid, skin, and intestine.² Histologically, MALT lymphomas are characterised by a proliferation of neoplastic marginal zone related cells that invade epithelial structures to generate lymphoepithelial lesions and colonise reactive lymphoid follicles.³ This acquired lymphoid tissue becomes genetically unstable, with the acquisition of structural abnormalities such as t(1;14)(BCL10-IGH),⁴ t(11;18)(API2-MALT1),^{5,6} t(14;18)(IGH-MALT1),⁷ and the most recently described t(3;14)(p14;q32) involving the immunoglobulin heavy chain locus (IGH) and FOXP1,⁸ as well as numerical aberrations such as trisomy 3 and trisomy 18,⁹ leading to transformation into MALT lymphoma.

In contrast to the preferential gastric occurrence, MALT lymphomas involving the gastrointestinal tract outside the stomach are relatively rare, and only single case reports or series including small numbers of patients have been published.^{3, 10–18} In early reports, a predilection for MALT lymphoma in the small intestine was postulated,³ but more recent reports of MALT lymphomas involving the colon and rectum have been accumulating.^{11–18} These lymphomas, however, were seen mostly in patients with disseminated disease, suggesting that the lesions found in the intestine might have been the result of secondary spread. The assumption that gastric lymphoma usually precedes the

intestinal lesions was further underscored by the findings of Du *et al*, who demonstrated clonal identity in concurrent gastric and intestinal MALT lymphomas with an accumulation of somatic mutations in the latter.¹⁶

The objective of our analysis was therefore to evaluate the extent of disease in all patients diagnosed with intestinal MALT lymphoma and to analyse the frequency of MALT lymphoma associated genetic changes—that is, t(11;18)(q21;q21), t(14;18)(q32;q21) involving IGH/MALT1, t(1;14)(p22;q32), and the numerical aberrations trisomy 3 and trisomy 18 in intestinal MALT lymphoma. Based on the assumption that intestinal MALT lymphoma manifestations are often associated with gastric MALT lymphoma, we were also interested in determining whether primary and secondary intestinal MALT lymphomas may be distinguished by their genetic profile.

METHODS

We studied 30 consecutive patients with a diagnosis of MALT lymphoma involving the intestine, initially diagnosed at our institution or referred for histological or clinical assessment. Information abstracted from the case records included the localisation of the lymphoma at initial diagnosis and the result of the staging procedures, which had to comprise at least computed tomography of the thorax and abdomen, gastroscopy with multiple biopsies, double contrast x ray of the small bowel, colonoscopy, and bone marrow biopsy. In

Abbreviations: BAC, bacterial artificial chromosome; FISH, fluorescence in situ hybridisation; MALT, mucosa associated lymphoid tissue; RT-PCR, reverse transcriptase polymerase chain reaction

Table 1 MALT lymphoma associated genetic aberrations in intestinal and gastric MALT lymphomas

Initial site	Additional sites	Age/sex	t(11;18)	Cen 3	Cen 18	BCL10
<i>Primary intestinal MALT lymphoma (n = 16)</i>						
Rectum		72/M	–	+3	–	t(1;14)
Sigmoid colon		70/M	–	–	–	t(1;14)
Colon	Appendix	70/M	–	+3	–	–
Colon	Caecum, ileum	57/M	–	+3	–	–
Colon	Caecum, appendix	81/F	–	+3	–	–
Ileum		57/M	–	+3	–	–
Rectum		49/F	–	+3	–	–
Rectum		78/F	–	+3	–	–
Rectum		60/F	–	+3	–	–
Duodenum		75/F	–	+3	+18	–
Duodenum		39/F	–	+3	+18	–
Colon		70/M	–	+3	+18	–
Rectum		73/F	–	+3,+3	–	–
Ileum	Regional lymph node	62/F	–	–	+18	–
Colon	Regional lymph node	71/M	A2048/M814	–	–	–
Jejunum		31/M	A2048/M541	–	–	–
<i>Secondary intestinal MALT lymphoma (n = 14)</i>						
Colon	Stomach*	68/M	–	+3	–	–
Colon	Stomach*	67/M	–	+3	–	–
Ileum	Stomach*	64/M	–	+3	–	–
Colon	Ileum, stomach*	83/M	–	+3	–	–
Duodenum	Stomach*	66/F	–	+3	–	–
Stomach	Caecum*	77/M	–	–	–	–
Stomach	Colon*	67/M	A2048/M814	–	–	–
Jejunum	Stomach*	62/M	A2048/M1150	–	–	–
Stomach 92†	Caecum, duodenum 01	63/F	A2048/M541	–	–	–
Stomach 93	Jejunum 96	62/M	A2048/M1123	–	–	–
Stomach	Duodenum, jejunum*	87/F	A2048/M1150	–	–	–
Lung	Colon*	73/M	A2048/M814	–	–	–
Stomach 85	Ileum, colon 00	66/M	A2048/M814	–	–	–
Rectum	Stomach*	71/M	A2048/M1150	–	–	–
<i>Primary gastric MALT lymphoma (n = 71)</i>						
Stomach			17 (24%)	8 (11%)	4 (6%)	0 (0%)

*Diagnosed at staging.

†92 refers to year of biopsy.

Cen, centromere specific probe for chromosome 3 or 18.

addition, 71 cases with primary gastric MALT lymphoma were analysed as a control group, and the findings were compared with the results obtained in patients with intestinal MALT lymphoma.

Formalin fixed, paraffin embedded tissue samples of biopsies or surgical resection specimens were retrieved from the authors' institutions. For inclusion in the analysis, the cases were required to fulfil the histological and immunohistological criteria defined for MALT lymphoma in the WHO classification of tumours of haematopoietic and lymphoid tissues.¹ The immunophenotype of the tumour cells—as assessed on paraffin sections—was CD20+, cyclin D1–, CD23–, CD5–, bcl-6–, CD10–.

The presence of tumour cells was evaluated in each tissue block on haematoxylin and eosin stained slides cut before and after the sections used for fluorescence in situ hybridisation (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) analyses.

RNA was isolated from archival formalin fixed, paraffin embedded lymphoma tissues. Total RNA was extracted from 10 µm sections with a high pure RNA paraffin kit (Roche Diagnostics, Mannheim, Germany). First strand cDNA was synthesised from 1 µg total RNA with a superscript first strand synthesis system (Invitrogen, Carlsbad, California, USA) using random hexamers as primers. RT-PCR for the detection of the *API2-MALT1* fusion transcript was undertaken according to Inagaki *et al*¹⁹ with one modification: first round RT-PCR products were amplified in a second round separately and not as multiplex nested PCRs, in order to discriminate the various fusion signals. Where indicated, PCR

products were sequenced using dRhodamine dye terminators on an ABI Prism 310 (PE Applied Biosystems, Foster City, California, USA).

Formalin fixed, paraffin embedded tissue was used for FISH. For a reliable interpretation of the hybridisation signals, we preferred the analysis of single cell suspensions to thin sections. FISH was undertaken on interphases with the following probe sets: for the detection of the t(14;18)(q32;q21) involving *IGH* and *MALT1*, we used P1 artificial chromosome (PAC) 152M5 (SpectrumOrange labelled) spanning the *MALT1* gene and flanking regions and bacterial artificial chromosome (BAC) 158A2; for rearrangements of *BCL10*, we used BACs RP11–1077C10 and RP11–36L4 (SpectrumGreen) centromeric to *BCL10* and RP11–1080I1 and RP11–40K4 (SpectrumOrange) telomeric to *BCL10*. In cases with rearrangement of *BCL10*, we used FISH with a dual colour, break apart rearrangement probe for *IGH* (Vysis, Downer's Grove, Illinois, USA); FISH with BAC 158A2 for *IGH* and BACs RP11–1080I1 and RP11–40K4 telomeric to *BCL10* was used to confirm the t(1;14)(p22;q32). For the detection of trisomies 3 and 18 we applied centromere specific probes for the chromosomes 3 (SpectrumOrange) and 18 (SpectrumGreen) (Vysis).

The cut off value for the diagnosis of each probe set was the mean percentage of cells with a false positive signal constellation plus 3 SD, as assessed on tissue from 20 reactive lymph nodes.

Differences in the frequency of chromosomal aberrations were investigated using the exact version of the χ^2 test. A two tailed probability (p) value of <0.05 was defined as significant.

Figure 1 Detection of t(11;18)(q21;q21) by reverse transcriptase polymerase chain reaction (RT-PCR) of the API2-MALT1 fusion transcript in primary intestinal, secondary intestinal, and primary gastric MALT lymphomas. In primary intestinal MALT lymphoma, t(11;18)(q21;q21) occurred in only two of 16 cases (12.5%), significantly fewer than in secondary intestinal MALT lymphomas (8 of 14, 57%) and primary gastric MALT lymphoma (17 of 71, 24%). RT-PCR results for only 16 of the 71 gastric lymphomas are shown. M, molecular marker; MALT, mucosa associated lymphoid tissue.

RESULTS

In all, 30 patients were identified from our records, and the minimum staging requirements were met in all cases. Ten of the 30 patients were staged according to Raderer *et al*¹² and additionally underwent ear, nose and throat investigation, and imaging of salivary and lacrimal glands. According to staging and follow up information, these 30 cases with intestinal MALT lymphoma involvement were divided into two groups: a homogeneous group comprising 16 cases of localised primary intestinal MALT lymphoma (five located in the small intestine and 11 in the large intestine) without further evidence of disease, and a heterogeneous group of 14 cases most probably representing secondary intestinal involvement caused by spread from gastric or pulmonary primaries (table 1). In the latter group, seven patients initially presented with intestinal lymphoma and were diagnosed as having gastric MALT lymphoma during subsequent staging. In the remaining patients, gastric (n = 6) and pulmonary (n = 1) lymphoma preceded the diagnosis of intestinal spread (for details see table 1).

The RT-PCR and FISH results are summarised in table 1. The t(11;18)(q21;q21) was found in 17 of 71 cases (24%) localised to the stomach, and in 10 of 30 cases (33%) in the whole group of patients with MALT lymphoma involving the intestine. Findings, however, were different between the two groups of intestinal MALT lymphomas, as two of 16 patients in the primary group (12.5%) were positive, as opposed to eight of 14 patients (57%) with secondary tumours. The secondary MALT lymphoma group therefore differed significantly from the primary intestinal and gastric MALT lymphoma groups by the high frequency of t(11;18)(q21;q21): 57% v 12.5%, $p = 0.019$, and 57% v 24%, $p = 0.022$ (fig 1).

Positivity by RT-PCR was confirmed by FISH in all cases which showed a split signal for *MALT1* but no *IGH/MALT1* fusion signals. Conversely, FISH did not identify a t(11;18)(q21;q21)+ case among those testing negative by RT-PCR, indicating 100% concordance of the two techniques. Furthermore, in the translocation positive cases two normal

signals were generated for *BCL10*—centromere 3 and centromere 18—indicating that t(11;18)(q21;q21) did not occur in combination with either t(14;18)(q32;q21) or *BCL10* rearrangement or either of the two trisomies. The distribution of breakpoints in both the *API2* and *MALT1* genes among MALT lymphomas of different sites was similar (data not shown) and also similar to those reported.²⁰

The t(14;18)(q32;q21) was identified in none of the intestinal lymphomas and in only one patient with gastric MALT lymphoma. This patient had already been included in a series of MALT lymphomas occurring in patients with Sjögren's syndrome, and is the first patient with a t(14;18)(q32;q21)+ gastric MALT lymphoma.²¹

A *BCL10* rearrangement was found in only two of the 101 cases, and *IGH* at band 14q32 represented the translocation partner in both cases. These two MALT lymphomas harbouring the t(1;14)(p22;q32) arose from the rectum and sigmoid colon and were among those judged to be primary intestinal lymphomas.

Trisomy 3 was observed in 75% of MALT lymphomas involving the intestine, while the overall incidence of trisomy 18 was lower, at 25% in this cohort of patients. The rate of trisomy 3 was 12/16 (75%) v 5/14 (36%) in primary and secondary intestinal MALT lymphomas, respectively, while that of trisomy 18 was 4/16 (25%) v 0/14. In contrast, the frequency of trisomy 3 (11.3%) and trisomy 18 (5.6%) was lower in the cohort of patients with localised gastric lymphoma. Primary intestinal MALT lymphomas were characterised by a significantly higher frequency of trisomies 3 and 18 (81% v 36%, $p = 0.024$, and 81% v 14%, $p < 0.001$, respectively), in contrast to secondary intestinal MALT lymphoma and localised gastric MALT lymphoma.

DISCUSSION

MALT lymphoma is one of the most common B cell neoplasms and arises by definition at an extranodal site. As a distinct disease entity listed in the WHO classification, the definition of MALT lymphoma is supposed to be a combination of morphology, immunophenotype, and genetic and

clinical features. While the genetic changes specific for or at least closely associated with the disease—that is, translocations t(1;14)(p22;q32), t(11;18)(q21;q21), and t(14;18)(q32;q21)—have been studied extensively in gastric MALT lymphoma, no analysis of their frequency in the less common intestinal MALT lymphomas has been undertaken. The major goal of the present study was therefore to analyse MALT lymphomas involving the intestine for all the three MALT lymphoma associated structural aberrations—t(11;18)(q21;q21), t(14;18)(q32;q21), and t(1;14)(p22;q32)—and additionally to screen for the most common numerical aberrations (trisomy 3 and trisomy 18).

Thirty patients with MALT lymphoma involving the intestine were identified from our records. In keeping with the notion that intestinal MALT lymphoma reflects secondary dissemination in a high proportion of patients, only 16 cases were judged to be primary MALT lymphomas by extensive staging. In the remaining 14 cases, seven initially presented with intestinal lymphoma and were diagnosed as having gastric MALT lymphoma during subsequent staging. In the other seven patients, gastric lymphoma (6) and pulmonary lymphoma (1) preceded the diagnosis of intestinal manifestations. Therefore, these data again underscore the importance of consequent staging in patients with MALT lymphoma, especially in those diagnosed with extragastric lymphomas.¹² A current problem in assessing disease extent, however, is the relative inaccessibility of the small intestine with standard staging. Thus discrete infiltrates might be still be missed and could be more accurately detected with capsule endoscopy²² or double balloon enteroscopy, which offers the potential advantage of obtaining biopsies for histological assessment.

The genetic analyses of the 16 primary and the 14 secondary intestinal MALT lymphomas clearly demonstrated striking differences among the two groups. All primary intestinal MALT lymphomas harboured at least one of the five aberrations examined, among which trisomies 3 and 18, separately or together, were the most prevalent, occurring in 13 of the 16 cases (81.5%), and might be regarded as a genetic hallmark of the disease. Conversely, we detected the t(11;18)(q21;q21) in only two of the 16 primary intestinal MALT lymphomas. Interestingly, Ye *et al* did not find the translocation in any of their 22 cases of immunoproliferative small intestinal disease, which by definition arises in the intestine and represents a variant of MALT lymphoma.¹²⁰ By contrast, secondary intestinal MALT lymphoma showed a significantly higher frequency of t(11;18)(q21;q21) which is not unexpected because of its association with primary gastric and hence more advanced disease. This finding might be of diagnostic and prognostic relevance because in the appropriate histological and immunohistological setting, t(11;18)(q21;q21) warrants very thorough examination of the stomach including multiple biopsies and endosonography to rule out gastric MALT lymphoma. The markedly different genetic profiles of primary intestinal and primary gastric MALT lymphoma—though detected in lesions arising in the same organ system, the gastrointestinal tract—most probably reflect different preceding diseases.

Aneuploidy, most commonly trisomy 3 or trisomy 18 or both, often occurs in MALT lymphoma.⁹ In our series, primary intestinal MALT lymphoma was characterised by significantly higher frequency of trisomy 3 or 18 (81% *v* 36%, *p* = 0.024; 81% *v* 14%, *p* < 0.001), in contrast to secondary intestinal MALT lymphoma and localised gastric MALT lymphoma. The high frequency of both numerical aberrations in primary intestinal MALT lymphomas suggests that one or more genes in chromosomes 3 and 18 are involved in the pathogenesis of these neoplasms. As opposed to t(11;18)(q21;q21), the presence of trisomies 3 and 18 appears

to be associated with localised intestinal disease. The presence of t(11;18)(q21;q21) in gastric lymphoma has repeatedly been reported as a negative prognostic factor in terms of lymphoma regression following *H pylori* eradication.²³ Interestingly, it has recently been suggested that t(11;18)(q21;q21) positive patients have a longer time to relapse than those without the translocation.²⁴ The current report, however, is the first to define trisomies 3 and 18 as genetic hallmarks of intestinal lymphoma. Because of the relative rarity of the disease, the potential prognostic implications of these genetic aberrations in intestinal MALT lymphoma have not been studied so far and should be addressed in future series involving larger numbers of patients.

Taken together, our data show that MALT lymphoma in the intestine reflects secondary spread from gastric MALT lymphoma in a high percentage of patients as judged by extensive staging. Primary intestinal MALT lymphoma, however, appears to be characterised by different genetic changes from secondary intestinal or localised gastric MALT lymphoma, probably reflecting a different pathogenesis.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1560

Multidetector computed tomography (MDCT) showed a mass at the jejunum with high density in the early arterial phase (fig 1). Angiography showed a hypervascular mass that was supplied by jejunal branches (fig 2). The patient underwent jejunal segmental resection. Histopathological assessment revealed a gastrointestinal stromal tumour (GIST) expressing C-kit and CD 34 (fig 3).

GISTs, frequently manifesting as gastrointestinal bleeding, are defined as mesenchymal neoplasms originating from the interstitial cells of Cajal that express the c-kit proto-oncogene protein (CD117) which is a cell membrane receptor with tyrosine kinase activity. The disease occurs mainly in the stomach and small intestine. MDCT angiography is useful for detecting the causes of obscure gastrointestinal bleeding^{1,2} and the vascularity of GIST that is related to malignancy.³ To date, however, the sensitivity and specificity of MDCT for diagnosis of the causes of obscure gastrointestinal bleeding

are not known, and further studies are needed.¹ Approximately 20–30% of GIST show malignant behaviour. Tumour size of >5 cm and >5 mitotic activities in 50-fold high power fields are useful predictors of malignancy. Surgery is the main modality of therapy and imatinib, a selective inhibitor of tyrosine kinases, can be used in metastatic or unresectable patients as neoadjuvant treatment.

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Figure 3 Immunohistochemical staining revealed a gastrointestinal stromal tumour expressing C-kit and CD 34.