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To cite this article: C. L. de Mol, M. A. W. Hermans, R. Gerth van Wijk, P. M. van Hagen & P. L. A. van Daele (2017): Routine abdominal ultrasonography has limited value in the care for patients with indolent systemic mastocytosis, Hematology, DOI: [10.1080/10245332.2017.1324377](https://doi.org/10.1080/10245332.2017.1324377)

To link to this article: <http://dx.doi.org/10.1080/10245332.2017.1324377>



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Accepted author version posted online: 26 Apr 2017.
Published online: 10 May 2017.



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Routine abdominal ultrasonography has limited value in the care for patients with indolent systemic mastocytosis

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ABSTRACT

Objectives: Systemic mastocytosis (SM) is a myeloproliferative disease characterized by the accumulation of aberrant mast cells. Since advanced subtypes of SM can lead to organ dysfunction and shortened survival, timely recognition of progressive disease is important for the adequate treatment of SM patients.

Methods: Here, we report the results of our cohort study on the value of routine abdominal ultrasonography for the detection of progression of indolent systemic mastocytosis (ISM).

Results: We included 88 patients with ISM, of whom 9 developed new hepatosplenomegaly during follow-up. In this group, the median serum tryptase level increased by 11.60 µg/l, compared with a decrease of -0.20 µg/l in the 79 patients with unchanged ultrasonography results ($p=0.016$). A change in liver and/or spleen size never led to a change in clinical classification, nor management.

Discussion: Based on the finding that a change in ultrasonography findings did not correlate to disease progression in general, it appears that isolated hepatosplenomegaly does not have prognostic implications in patients with ISM.

Conclusions: Routine abdominal ultrasonography is redundant in the follow-up of patients with ISM. A combination of physical examination with serum tryptase levels can be used to screen for hepatosplenomegaly.



KEYWORDS

Indolent; mastocytosis; hepatosplenomegaly; abdominal; ultrasonography; tryptase

Introduction

Mastocytosis is a rare myeloproliferative disease in which there is uncontrolled proliferation of aberrant mast cells [1]. The World Health Organisation (WHO) distinguishes cutaneous from systemic mastocytosis [2]. Systemic mastocytosis (SM) is further divided into different subtypes, each having their own criteria, clinical manifestations and prognosis [3,4]. Indolent systemic mastocytosis (ISM) is the most common subtype which has a favourable prognosis, with patients mainly suffering from mast cell mediator-related symptoms. More recently, it was recognized that the clinical symptoms of ISM patients with skin lesions are distinct from the ISM patients without skin lesions (ISM_s+ vs. ISM_s-, respectively) [5]. In contrast to ISM, advanced subtypes are characterized by organ infiltration by mast cells (smouldering SM and aggressive SM), or a second haematological (non-mast cell) neoplasm (SM-AHN). To diagnose smouldering SM, 2 or more B-findings have to be present: hepato- or splenomegaly, lymphadenopathy, >30% mast cell infiltration of bone marrow, a serum tryptase level >200 µg/l, or signs of dysplasia without reaching criteria for myelodysplastic syndrome. For aggressive

SM, C-findings were formulated: cytopaenia, signs of liver cirrhosis, malabsorption or osteolytical bone lesions. The difference between smouldering and aggressive SM is the respective absence or presence of organ dysfunction. These advanced subtypes can shorten survival and often warrant cytoreductive treatment [4,6]. Hence, an important goal of outpatient follow-up of ISM patients is to screen for progression of the disease or development of a second haematological disease [3]. There is some evidence that radiological examination of the abdomen can aid in determining the extent of systemic involvement of SM [7]. For these reasons, a consensus group of Dutch physicians with expertise in mastocytosis previously decided to routinely perform abdominal ultrasonography in the follow-up of SM patients. In the Erasmus University Medical Centre, it was common practice to perform abdominal ultrasonography every 2–3 years to screen for hepatosplenomegaly. However, new data show that progression of indolent to advanced SM is rare, and it is unclear what would be the best method to screen patients with ISM for progression. Moreover, in this era where health care costs are an important societal issue, it is important to cut

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down unnecessary tests. The objective of this study was, therefore, to determine the value of routine abdominal ultrasonography as a tool to screen for progression of indolent to more aggressive forms of SM.

Methods

Patient selection and data collection

We selected all adult patients who visited the Erasmus University Medical Centre from January 2009 to February 2016 and who fulfilled the WHO criteria for ISM [2]. Only patients who underwent at least two abdominal ultrasonographies, with a minimal interval of 2 years, were included. Patients who had SM-AHN or ASM at baseline were excluded. All patients visited the outpatient clinic at least once a year. Bone densitometry was performed every 3 years to screen for osteoporosis. We retrospectively collected the findings on abdominal ultrasonography, as well as data on patient baseline characteristics, SM subtype and symptoms, tryptase levels, and bone densitometry results from the electronic patient charts.

Definitions

Hepatosplenomegaly was defined as either a craniocaudal liver size of >15 cm, and/or a spleen size of >11 cm. A change in ultrasonography findings was defined as a change from a normal size to hepatosplenomegaly on subsequent examinations, or vice versa. Cytopenia was defined as either anaemia (Hb <10 g/dl),

leukopenia ($<400 \times 10^6$) and/or thrombocytopenia ($<1000 \times 10^6$). Skin involvement was described as all forms of maculopapular cutaneous mastocytosis (MPCM) [8].

Statistical analysis

We constructed two groups, according to their course of ultrasonography results. The primary endpoint was progression from indolent to smouldering, aggressive or SM-AHN, or progression from smouldering to aggressive or SM-AHN. We used IBM SPSS statistics 21 for all analyses. The Mann–Whitney U-test was used for the comparison of the tryptase values and unpaired *t*-tests were used for continuous variables. The chi-square test was used for dichotomous variables.

Results

Study population

Of a total of 154 patients, 95 underwent multiple abdominal ultrasonographies with an interval of ≥ 2 years. Seven patients were excluded because they fulfilled the WHO criteria for ASM or SM-AHN at baseline. Figure 1 summarises the selection process. The population we analysed thus consisted of 88 patients, of whom 81 had ISM and 7 patients had smouldering SM. Ten of these 88 patients had a change in liver and/or spleen size over time, 9 of whom newly developed hepatosplenomegaly (10.2% of the total

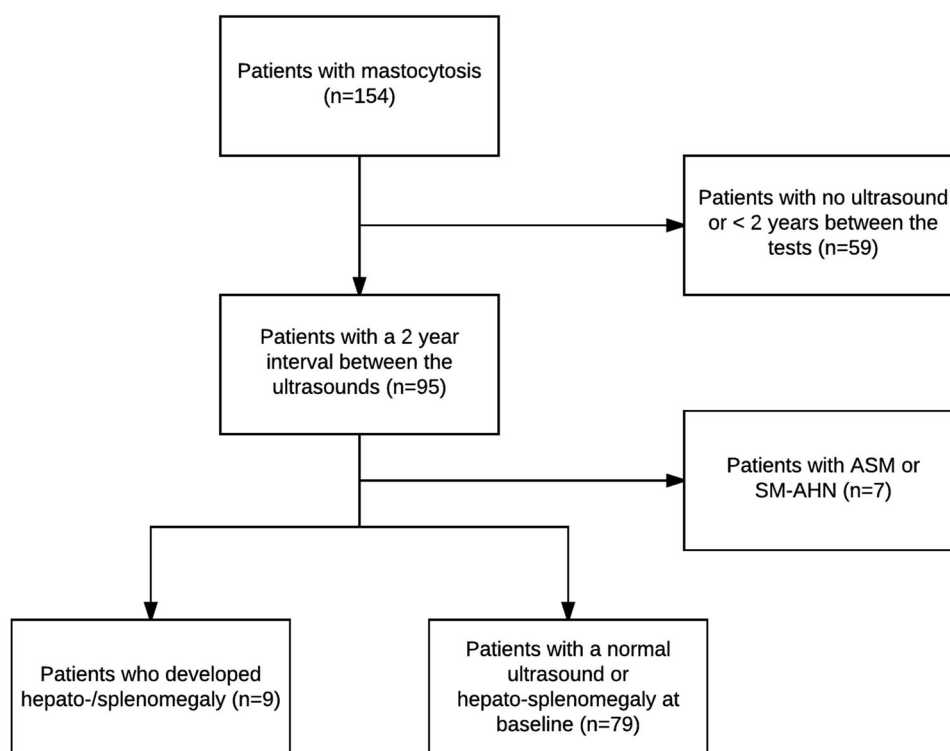


Figure 1. Flow chart of the inclusion process.

Table 1. Patient characteristics, divided according to ultrasonography findings.

	Unchanged status of hepatosplenomegaly (n = 79)	New hepatosplenomegaly (n = 9)	p-value
Age in years (median, SD)	58.00 (12.89)	54.00 (9.94)	NS
Male sex (n, %)	35 (44.3%)	3 (33.3%)	NS
Follow-up time in years (median, SD)	10.00 (6.76)	12.00 (3.24)	NS
Subtype of SM			N/A
ISM s–	17	2	
ISM s+	56	6	
SSM	6	1	
Absolute change in serum tryptase levels in µg/l (median, SD)	–0.20 (28.3)	11.60 (26.2)	0.016
Change in subtype (n)	1	0	N/A
Change in treatment (n)	0	0	N/A
Cytopaenia at baseline (n, %)	2 (2.5%)	0 (0%)	NS
Decrease in bone density during follow-up (n, %)	11 (13.9%)	0 (0%)	NS
Presence of KIT D816V mutation (n, %)	36 (45.5%)	4 (44.4%)	NS
Presence of lymphadenopathy (n, %)	4 (5.1%)	0 (0%)	NS

Note: SD: standard deviation; SM: systemic mastocytosis; ISM s–: indolent systemic mastocytosis without skin lesions; ISM s+: indolent systemic mastocytosis with skin lesions; SSM: smouldering systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematological neoplasm; ASM: aggressive systemic mastocytosis; NS: non-significant, N/A: not applicable.

population). The liver and spleen size normalized in one patient. The median follow-up time was 11.20 years.

Group characteristics

We divided the population into two groups, entitled ‘unchanged hepatosplenomegaly status’ and ‘new hepatosplenomegaly’. Baseline characteristics and follow-up data are summarized in Table 1. The patient with normalization of liver/spleen size was included in the ‘unchanged hepatosplenomegaly status’ group. The age of the patients did not differ significantly between the two groups. Two patients in the ‘unchanged hepatosplenomegaly status’ group had cytopaenia at baseline. No one had other B- or C-findings. The development of hepatosplenomegaly during follow-up was not associated with a decrease in bone density.

Follow-up findings

The median change in serum tryptase level during follow-up was –0.20 µg/l (SD 28.3) for the ‘unchanged hepatosplenomegaly status’ group, versus an increase of 11.60 µg/l (SD 26.2) in the ‘new hepatosplenomegaly’ group. When comparing the change in tryptase levels over time, a significant difference was found between the patients who newly developed hepatosplenomegaly compared with the patients with unchanged ultrasonography findings ($p=0.016$). In the patients who newly developed hepatosplenomegaly, there was no statistically significant change in liver enzyme levels (mean increase in ASAT levels of 4 U/l (SD 11.86 U/l), mean increase in ALAT levels of 7.5 U/l (SD 22.05 U/l)).

Of the patients with ‘unchanged hepatosplenomegaly status’, 12 (15.2%) had hepatosplenomegaly at baseline which did not change during follow-up. These patients did not develop clinical signs of liver

cirrhosis during follow-up, nor did they show other signs of progression of mastocytosis. Accordingly, serum tryptase levels remained relatively stable with a median decrease of –1.15 µg/l (SD 48.0 µg/l) in this subgroup.

One patient in the unchanged group went from ISM s+ to smouldering SM over time, based on a serum tryptase level of >200 µg/l and >30% bone marrow infiltration by mast cells. This patient had no hepatosplenomegaly. A change in liver and/or spleen size alone never led to a change in SM subtype, nor in a change in the medical management. One patient showed normalization of his liver size and spleen size. This patient was treated with imatinib because of extensive skin lesions. In this patient, the KIT D816 V mutation was detected and his tryptase value increased by 6.0 µg/l during follow-up.

Discussion

This study shows that routine abdominal ultrasonography has limited value in the follow-up of patients with indolent systemic mastocytosis: 10.2% developed new hepatosplenomegaly, but no one showed progression to a more advanced type of SM. The development of new hepatosplenomegaly had no clinical consequences in any of them. Until this study, abdominal ultrasonography was part of the routine follow-up in the Erasmus University Medical Centre to screen for progression of ISM. However, it has become clear that progression of ISM is very rare [3,9]. Our results confirm this, as only one patient (1.1%) progressed from indolent to smouldering SM in a median follow-up time of 11.20 years. Moreover, this patient did not develop hepatosplenomegaly. Furthermore, patients who had hepatosplenomegaly at baseline did not develop clinical signs of liver cirrhosis, or progression of mastocytosis in general. Based on these findings, we hypothesize that the finding of isolated hepatosplenomegaly, without

other B- or C-findings, does not have important prognostic implications. Therefore, looking for hepatosplenomegaly is probably not appropriate when screening for progression of disease in ISM. Moreover, badly indicated radiologic investigations lead to higher health care costs, and a risk of unwanted incidental findings [10]. Interestingly, the median serum tryptase level increased significantly in patients who newly developed hepatosplenomegaly, whereas they remained stable in patients with unchanged ultrasonography findings. Besides the serum tryptase level, there were no other signs of progression of disease in all patients but one who progressed from indolent to smouldering SM. More specifically, patients did not develop other B- or C-findings. In another study, serum tryptase levels did correlate to clinical progression in general, and patients with rising serum tryptase levels more often developed hepatosplenomegaly [11]. It would be interesting to know whether the hepatosplenomegaly truly is mast cell related; however, this would require biopsies of both organs which is a risky procedure and not feasible in this context. Furthermore, MR elastography or fibroscan could be of additional value to estimate a risk of liver cirrhosis in the future. Unfortunately, we have not performed these investigations routinely and cannot provide data on this yet [12].

To our knowledge, our study is the first to focus on the value of routine abdominal ultrasonography in the screening for progression of disease in ISM patients. However, our results should not be extrapolated to patients with advanced subtypes of SM. Follow-up abdominal ultrasonography can be indicated in advanced SM for other reasons. One limitation of this study is the retrospective nature, which could have led to incomplete data. We had to exclude 59 patients, because they did not have ≥ 2 abdominal ultrasonographies during follow-up. This could have led to a selection bias, although the fact that their physician did not order more ultrasonographies probably implies that they estimated the risk of progression as low. In that scenario, our results would not have changed with inclusion of these patients. Moreover, the retrospective design provides 'real-life' data and a long follow-up time. Lastly, ultrasonography, in general, has a notoriously large inter-test variability and one can argue whether subtle cases of hepatosplenomegaly were missed by using this technique [13].

In conclusion, routine abdominal ultrasonography has limited value as a screening tool for progression of ISM. It appears that isolated hepatosplenomegaly has no important prognostic implications in ISM, and changes in liver and/or spleen size alone, in fact, never herald progression of SM. Moreover, progression of indolent to advanced SM is very rare. Annual follow-up of serum tryptase levels could be used as a first screening tool for the development of

hepatosplenomegaly, with additional radiologic studies on indication.

Disclosure statement

No potential conflict of interest was reported by the authors.

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