

Mixed-lineage eosinophil/basophil crisis in MDS: a rare form of progression

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ABSTRACT

Background Basophilic crisis and eosinophilia are well recognized features of advanced chronic myeloid leukaemia. In other myeloid neoplasms, however, transformation with marked basophilia and eosinophilia is considered unusual.

Design We examined the long-term follow-up of 322 patients with *de novo* myelodysplastic syndromes (MDS) to define the frequency of basophilic, eosinophilic and mixed lineage (basophilic and eosinophilic) transformation.

Results Of all patients, only one developed mixed lineage crisis ($\geq 20\%$ basophils and $\geq 20\%$ eosinophils). In this patient, who initially suffered from chronic myelomonocytic leukaemia, basophils increased to 48% and eosinophils up to 31% at the time of progression. Mixed lineage crisis was not accompanied by an increase in blast cells or organomegaly. The presence of BCR/ABL and other relevant fusion gene products (FIP1L1/PDGFR α , AML1/ETO, PML/RAR α , CBF β /MYH11) were excluded by PCR. Myelomastocytic transformation/myelomastocytic leukaemia and primary mast cell disease were excluded by histology, *KIT* mutation analysis, electron microscopy and immunophenotyping. Basophils were thus found to be CD123+, CD203c+, BB1+, *KIT*-cells, and to express a functional IgE-receptor. Among the other patients with MDS examined, 4 (1.2%) were found to have marked basophilia ($\geq 20\%$) and 7 (2.1%) were found to have massive eosinophilia ($\geq 20\%$), whereas mixed-lineage crisis was detected in none of them.

Conclusions Mixed basophil/eosinophil crisis may develop in patients with MDS but is an extremely rare event.

Keywords Basophils, eosinophils, MDS, prognosis

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Introduction

Basophilia and eosinophilia are typical features of myeloproliferative neoplasms (MPN). In chronic myeloid leukaemia (CML), basophilia with or without coexisting eosinophilia is a characteristic finding and is of prognostic significance [1–3]. In addition, basophils typically increase in number during acceleration in CML [1–6]. In some of these patients, an excessive accumulation of basophils is found. The clinical condition in these patients has been referred to as ‘basophil crisis’ or ‘secondary basophilic leukaemia’ [7–10]. In other myeloid neoplasms, ‘basophil crisis’ is an extremely rare event. In some of these cases, basophilia is a misdiagnosis as these cells are mast cells which can be demonstrated by immunophenotyping or electron microscopy [11–14]. Therefore, it is of great importance to define whether metachromatic cells in transformed myeloid neoplasms are derived from the basophil

or the mast cell lineage [11–16]. Another differential diagnosis is mast cell leukaemia, which may also be accompanied by eosinophilia [16–18].

In chronic myelomonocytic leukaemia (CMML), now regarded as an overlap (mixed myeloproliferative/myelodysplastic) disease, eosinophilia and basophilia have also been described [19–21]. However, in most cases, the numbers of basophils and/or eosinophils were not reported to be extensively high, and did not further increase during progression. In fact, in most cases, leukaemic transformation in CMML is accompanied by an increase in blasts outnumbering basophils and other leukocytes.

We present an unusual case of CMML in whom bi-lineage crisis with an excessive increase in basophils and eosinophils developed.

Table 1 Time course of blood counts and differential counts in the patient with mixed-lineage eosinophil/basophil crisis

Parameter	Time of investigation							
	April 1997	April 1998	April 2001	May 2003	December 2003	December 2004	August 2005	October 2005
Hb (g dL ⁻¹)	11	9.3	10.1	10.1	8.9	8.6	10.6	11.3
WBC (G L ⁻¹)	8.95	11.35	12.85	15.49	19.1	36.3	74.95	34.24
Segmented (%)	42	49	37	28	23	19	13	5
Band forms (%)	1	1	1	9	0	0	5	1
Eosinophils (%)	1	1	0	7	28	25	29	25
Basophils (%)	1	0	2	6	22	36	41	44
Monocytes (%)	19	12	20	19	13	8	8	11
Lymphocytes (%)	32	30	34	26	14	12	4	12
Atypical Lymphocytes (%)	0	0	0	0	0	0	0	1
LGL (%)	2	0	0	2	0	0	0	0
Metamyelocytes (%)	0	4	5	0	0	0	0	0
Myelocytes (%)	0	3	1	3	0	0	0	1
Promyelocytes (%)	0	0	0	0	0	0	0	0
Blasts (%)	0	0	0	0	0	0	0	0

Hb, hemoglobin; WBC, white blood count; LGL, large granular lymphocytes.

Patients and methods

Patients

A total number of 322 patients with *de novo* MDS seen at our department, were examined (females $n = 136$, males $n = 186$; ratio f/m 1 : 1.4; median age: 71, range: 24–92). All patients had a follow-up with serial determinations of blood counts and differential counts. The median observation time was 17 months (range 1.2–159.5 months). According to French-American-British (FAB) criteria [22,23], 102 patients (31.7%) had refractory anaemia (RA), 63 (19.6%) RA with ringed sideroblasts (RARS), 72 (22.4%) RA with excess of blasts (RAEB), 53 (16.4%) with RAEB in transformation (RAEB-T), and 32 (9.9%) CMML. Data were analyzed retrospectively. Most patients were treated with supportive therapy. Of all patients examined only one developed mixed lineage eosinophil/basophil crisis.

Case report

A 76 year old female patient first presented in March 1997 because of normochromic anaemia (Hb 8.1 g dL⁻¹) and leukocytosis (17 600 μL^{-1}). Physical examination disclosed normal results (no splenomegaly). The differential count showed a mild left shift without eosinophilia or basophilia. The bone marrow biopsy and aspirate showed a hypercellular marrow with dysplasia and an increase in partly immature monocytes but no increase in blasts. The diagnosis CMML was established. The

follow-up revealed a stable disease with constant leukocyte and monocyte counts, stable platelet counts and low transfusion frequency (10 red cell concentrates between 1997 and 2005). Basophil and eosinophil counts remained normal until 2003. In December 2003 a marked increase in circulating metachromatic cells (22% = 4200 μL^{-1}) was detected [Table 1]. In addition, an increase in eosinophils was recorded whereas monocytes decreased and no circulating blast cells were found. Basophilia and eosinophilia persisted during the observation period without other signs of progression. In April 2005 basophils increased to 48%. A second bone marrow examination was performed and revealed an increase in basophils, eosinophils and monocytic progenitors without an increase in blasts or signs of mastocytosis. Electron microscopy and immunophenotyping confirmed the presence of basophils and excluded the presence of mast cells.

Molecular studies and cytogenetics

Karyotyping was performed on Giemsa-banded metaphases of leukaemic cells (MNC) as described [24]. A multiplex reverse transcription (RT) PCR (mDx-HemaVision, Bio-Rad Laboratories, Hercules, CA, USA) was performed on bone marrow MNC to seek for fusion gene products related to the following karyotypes: t(X; 11), t(4,11), t(6,11), t(11,19), t(10,11), t(1,11), t(11,17), t(9,11), t(1,19), t(17,19), t(12,21), t(8,21), t(3,21), t(16,21), t(15,17), t(5,17), t(6,9), t(9,9), inv(16), t(9,22), t(9,12), t(5,12), t(12,22), t(3,5).

Table 2 Specification of antibodies and immunohistochemical staining techniques applied

CD	Antibody (clone*)	Reactive antigen	Ig class	Source	Dilution	Retrieval technique†
n.c.	BB1	Basogranulin	IgG2a	mouse	1:500	Prot
n.c.	2D7	2D7	IgG1	mouse	1:500	Prot
CD9	72F6	MRP-1	IgG1	mouse	1:200	MW
CD34	QBEND10	HPCA-1	IgG1	mouse	1:100	MW
CD63	NKI/C3	MEA	IgG	mouse	1:50	MW
CD117	α KIT	KIT/SCFR	poly	rabbit	1:150	MW
n.c.	polyclonal	HDC	poly	rabbit	1:1000	MW
n.c.	G3	Tryptase	IgG1	mouse	1:5000	–

*clone of monoclonal antibody; HPCA-1, haematopoietic progenitor cell antigen-1; SCFR, stem cell factor receptor; n.c., not yet clustered.

†Retrieval techniques: MW, microwave oven; Prot, proteinase type XXIV.

In addition, neoplastic cells were examined for the presence of the *KIT* D816V mutation and the *FIP1L1/PDGFERA* fusion gene as reported [25–27].

Flow cytometry

To define the cell surface marker profile and thus lineage involvement (basophils versus mast cells), multicolour flow cytometry was performed as reported [28,29]. For basophil detection, the phycoerythrin (PE)-labelled basophil-specific monoclonal antibody (mAb) 97A6 (CD203c) (Immunotech, Marseille, France) was applied. Additional mAbs used were mIgG1-FITC (MOPC-21), mIgG1-PE (MOPC-21), CD34-FITC (581), and CD123-PE (9F5), all from Becton Dickinson (San Diego, CA, USA), CD117-APC (104D2D1) and anti-IgE antibody E124-2-8 (D ϵ 2) from Immunotech, and goat F(ab')₂ antimouse IgG(H + L)-FITC from Caltag (Burlingame, CA, USA). Whole blood cells were stained with antibodies (10 μ L each) for 15 min. Thereafter, cell samples were subjected to erythrocyte-lysis with 2 mL FACSTM Lysing Solution (Becton Dickinson). Cells were then washed, resuspended and analyzed on a FACSCalibur (Becton Dickinson). In select experiments MNC were used.

Immunohistochemistry (IHC) and immunocytochemistry (ICC)

Bone marrow specimens were fixed in an ethanol-formaldehyde solution, followed by decalcification in EDTA and embedding in paraffin. Sections of 2 μ m were cut, dewaxed in xylene, and treated with 0.3% methanol-H₂O₂ to block endogenous peroxidase. IHC was performed using the avidin-biotin immunoperoxidase staining technique as described [30–34]. The following antibodies were applied: antitryptase mAb G3 (Chemicon, Temecula, CA, USA), a polyclonal anti-KIT antibody (Dako, Copenhagen, Denmark), the CD34 mAb QBEND10 (Immunotech), the

basophil specific mAb 2D7 [35] kindly provided by Dr L. B. Schwartz (Virginia Commonwealth University, Richmond, VA, USA), the antibasogranulin mAb BB1 [36] kindly provided by Dr A. F. Walls (University of Southampton, Southampton, UK), the CD9 mAb 72F6 and the CD63 mAb NKI/C3 (Novocastra, Newcastle upon Tyne, UK), and an antibody against histidine decarboxylase (anti-HDC; Progen, Heidelberg, Germany). The antibodies used and the staining techniques applied are depicted in Table 2. As chromogen, 3-amino-9-ethyl-carbazole (AEC) was used. For ICC, MNC were spun on cytospin slides, fixed in acetone, and stained with antibodies (BB1, 2D7, G3, and QBEND10) as reported [33].

Electron microscopy (EM)

EM was performed on blood MNC according to a published protocol [38,39]. In brief, 2×10^6 MNC were washed, fixed in 1% paraformaldehyde, 1.25% glutaraldehyde and 0.025% CaCl₂ buffered in 0.1 M sodium cacodylate buffer (pH 7.4). Cells were then washed in cacodylate buffer, suspended in 2% agar and centrifuged. Pellets were post-fixed with 0.66 M collidine-buffered 1.3% OsO₄, and stained en bloc with 2% uranyl acetate in sodium maleate buffer (pH 4.4) for 2 h. Pellets were then rinsed, dehydrated in an alcohol series, and embedded in EPON 812. Ultra thin sections were cut, placed on copper grids, and contrasted in uranyl acetate and lead citrate. Grids were viewed in a JEOL 1200 transmission electron microscope (Tokyo, Japan).

Histamine release experiments

Histamine release was performed essentially as reported [39]. In brief, basophils were washed and resuspended in histamine release buffer (HRB) (Immunotech). Then, cells were challenged with anti-IgE antibody E124-2.8 (Immunotech) (0.01–1 μ g mL⁻¹)

Table 3 Characteristics of patients with a marked increase in basophilic cells

#	Age (years)	m/f	FAB at diagnosis	FAB at the time of marked basophilia	WBC ($G L^{-1}$)	Eosinophils (%)	Basophils (%)	LDH ($U L^{-1}$)	Splenomegaly palpable yes/no	Therapy	Survival/LFU (months)*
1	75	m	RARS	RARS	2.6	1	10	153	no	–	46
2	59	m	CMML	CMML	87.0	0	12	164	yes	CT, HU	17
3	54	f	CMML	CMML	35.2	4	11	273	yes	CT, HU	19
4	58	m	RARS	RARS	4.3	4	10	138	no	–	88
5	67	m	RAEB-T	RAEB-T	8.3	3	13	394	no	–	2
6	81	m	RA	RA	5.1	1	12	259	no	–	10
7	65	m	RAEB	RAEB†	4.2	7	25	154	yes	–	6
8	74	m	CMML	CMML	13.9	0	17	235	yes	HU	Alive (51)
9	68	m	RA	AML	6.6	7	13	333	yes	HU	34
10	67	m	RAEB	RAEB	2.2	4	10	187	no	Lenalidomide	Alive (38)
11	61	m	RA	RAEB-T	10.3	3	12	782	not known	HU	31
12	76	m	RAEB	RAEB†	3.6	5	20	275	no	CT	5
13	76	m	RAEB-T	RAEB-T	4.2	0	12	222	no	CT	LFU (4)
14	82	f	CMML	CMML	10.8	8	10	236	no	HU	LFU (96)

*The median overall survival in all patients with MDS analysed ($n = 322$) was 17 months, and exactly the same result was obtained when analysing all MDS patients without marked basophilia ($n = 308$): 17 months median overall survival.

†In these 2 patients, 'basophilic' cells were found to be mast cells by immunophenotyping.

Abbreviations. m, males; f, females; FAB, French-American-British classification; WBC, white blood count; LDH, lactate dehydrogenase; CT, chemotherapy; HU, hydroxyurea; LFU, lost for follow-up.

in HRB at 37 °C. Thereafter, cells were centrifuged at 4 °C, and cell free supernatants and cell pellets recovered. Histamine was measured by radioimmunoassay (Immunotech). Release was expressed as a percentage of total (extra + intracellular) histamine.

Results

Frequency of basophilia and eosinophilia in MDS

The median overall survival of all patients with MDS amounted to 17 months. Of all 322 patients, 14 (4.3%) were found to have or to develop a marked increase in basophilic cells ($\geq 10\%$ of peripheral blood cells) [Table 3], and 29 patients (9.0%) had or developed eosinophilia ($\geq 10\%$). Massive basophilia ($\geq 20\%$) was detectable in five patients (1.6%), and massive eosinophilia ($\geq 20\%$) in eight patients (2.5%). Only one patient was found to develop both an excess in basophils ($\geq 20\%$) and excessive eosinophilia ($\geq 20\%$). This patient was found to have CMML (see case report). Among all CMML patients ($n = 32$) only one (this) CMML patient (3.1%) developed a marked increase in both eosinophils and basophils. In MDS patients with marked or excess basophilia, metachromatic cells were subjected to electron microscopy and/or immunophenotyping. In most cases (12/14), the presence of basophils could be demonstrated. However, in two patients,

metachromatic cells were found to be mast cells or mast cell progenitors (#7 and #12 in Table 3), leading to the final diagnosis of myelomastocytic leukaemia [11,12].

Morphologic examination and ultrastructure of neoplastic cells in the patient with mixed-lineage crisis

Wright Giemsa-staining of peripheral blood MNC revealed a mixture of lymphocytes, monocytic progenitors, a few eosinophils and numerous metachromatic cells. These metachromatic cells were found to have segmented nuclei and medium-sized metachromatic granules (Fig. 1a). Most of the cells were thus classified as basophil granulocytes. However, in a smaller proportion of cells, it was impossible to decide whether they were basophils or mast cells. However, EM confirmed that all metachromatic cells were within the basophil lineage. In fact, no mast cells or mast cell progenitors were detected by EM. Figure 1b shows a basophilic granulocyte detected by EM in our patient with mixed-lineage transformation.

Expression of leukocyte differentiation antigens in blood basophils

In a next step, metachromatic cells were examined for expression of leukocyte differentiation antigens using antibodies directed against basophil-related and mast cell-related surface antigens,

Figure 1 Morphology and ultrastructure of metachromatic cells. (a) Wright-Giemsa stain of metachromatic cells obtained from the patient's peripheral blood. The cells were found to exhibit segmented nuclei and numerous basophilic granules. (b) Electron microscopy of metachromatic cells confirmed the presence of basophils. Note that these cells contained particulate granules (arrows) typically found in basophil granulocytes. Mast cells were not detected by electron microscopy.

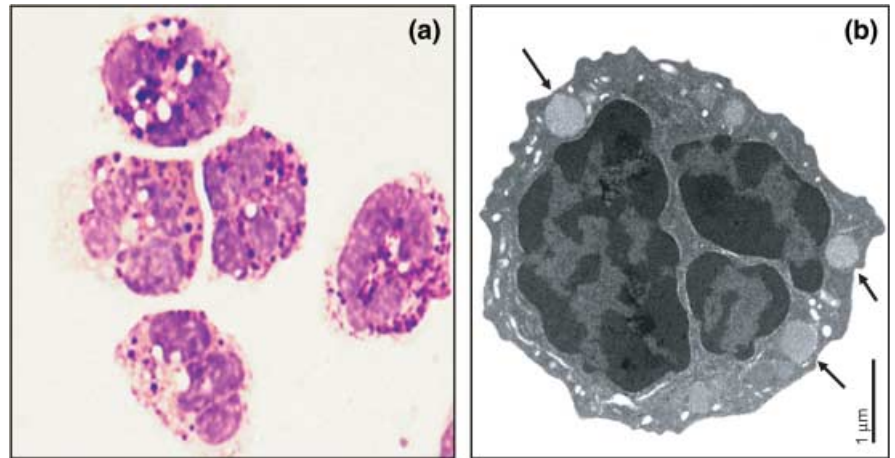


Figure 2 Surface marker profile of leukaemic basophils. Co-expression of surface molecules was analyzed by multicolour flow cytometry using antibodies against CD117, CD123, and CD203c as described in the text. Typical dot blots obtained in multi-colour staining experiments are shown. As visible, basophils displayed CD203c and CD123, but did not express substantial amounts of KIT, corresponding with the phenotype of normal human blood basophils.

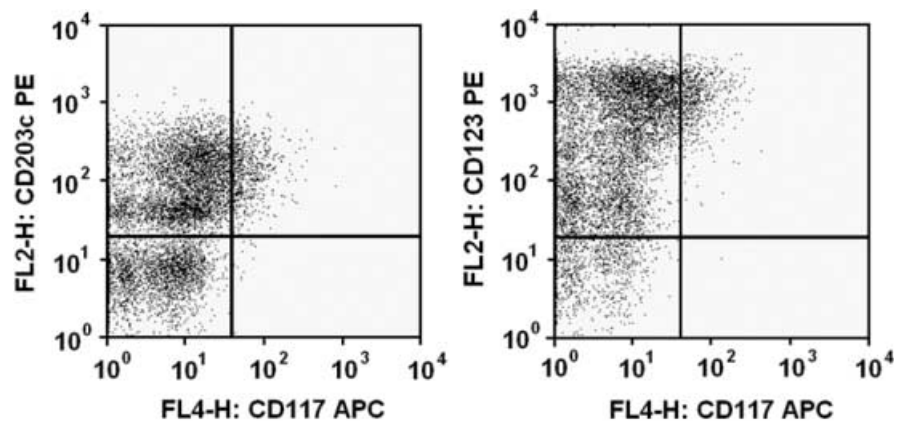


Table 4 Reactivity of leukaemic basophils with monoclonal antibodies

Antigen	CD	Technique	Reactivity of basophils with antibodies
KIT/SCFR	CD117	IHC, ICC, FC	–
Tryptase	n.c.	IHC, ICC	+/-
HDC	n.c.	IHC	+
Basogranulin	n.c.	IHC, ICC	+
2D7	n.c.	IHC, ICC	+
MRP-1	CD9	IHC	+
MEA	CD63	IHC	+
HPCA-1	CD34	IHC, ICC, FC	–
E-NPP3	CD203c	FC	+
IL-3RA	CD123	FC	+

IHC, immunohistochemistry; ICC, immunocytochemistry; FC, flow cytometry; HDC, histidine decarboxylase; n.c., not yet clustered.

and multicolour flow cytometry. Metachromatic cells displayed CD123 as well as CD203c, but did not express substantial amounts of CD34 or CD117 [Fig. 2, Table 4]. This marker profile corresponds with the cell surface phenotype of basophils [15,40] and excluded the presence of mast cells. The presence of basophils was also confirmed by immunocytochemistry and immunohistochemistry. In fact, leukaemic metachromatic cells were found to react with antibodies against 2D7, and basogranulin (BB1), but did not react with antibodies against KIT. Finally, we sorted neoplastic CD203c+ cells, and asked whether these cells are indeed basophils. Sorted CD203c+ metachromatic cells were all basophils and displayed metachromatic granules by Giemsa staining.

Detection of the IgE receptor on leukaemic basophils

To provide further evidence for the presence of basophils, we examined expression of the IgE-receptor on leukaemic cells. In a first step, we were able to show that leukaemic basophils display surface-bound IgE by flow cytometry (Fig. 3a). In a second step, the IgE receptor on basophils was cross-linked by

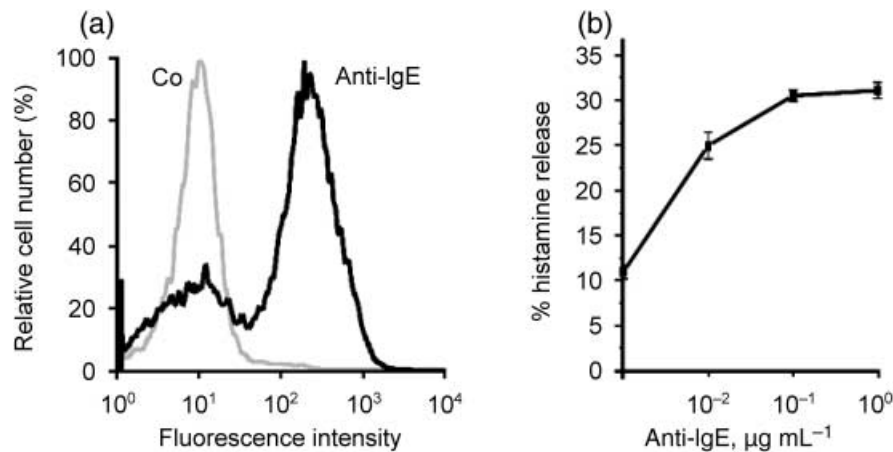


Figure 3 Expression of the IgE receptor on neoplastic basophils. (a) Blood basophils were stained with an antibody against IgE as described in the text. As visible, basophils displayed cell-bound IgE suggesting the presence of the high affinity IgE receptor (Fc epsilon receptor I). (b) Basophils were incubated with increasing concentrations of anti-IgE antibody E124.2.8 (as indicated) in histamine release buffer at 37 °C and 5% CO₂. After 30 minutes, cells were centrifuged in the cold and cell-free supernatants and pellets recovered. Histamine was measured by radioimmunoassay. Histamine release is expressed as a percentage of total histamine, results representing the mean $\pm$ S.D. from triplicate determinations.

exposure to an anti-IgE antibody (E124.2.8) at 37 °C for 30 min. As visible in (Fig. 3b), IgE-receptor-cross-linking was followed by dose-dependent release of histamine.

Karyotyping, molecular analyses and colony forming units

Chromosome analysis of bone marrow MNC was performed in 2005 and revealed a normal karyotype (46,XX). Molecular analyses were performed to seek for leukaemia-specific fusion gene-products including BCR/ABL and FIP1L1/PDGFR α . However, as assessed by multiplex PCR and conventional PCR, no leukaemia-specific fusion gene products could be detected. In addition, no *KIT* mutation D816V, usually found in systemic mastocytosis [25,41,42], was detected.

Measurement of tryptase

Serum tryptase levels were measured in June 1999 as well as at the time of transformation (July 2004, March 2005, April 2005, June 2005) by fluoroimmunoassay (Phadia, Uppsala, Sweden). In June 1999, the tryptase level amounted to 24 ng mL⁻¹. Interestingly, no further increase in tryptase levels were seen during transformation (June 2005: 22 ng mL⁻¹).

Clinical course

During evolution into eosinophil/basophil-crisis, no increase in blast cells was found. Palliative therapy with hydroxyurea was started in August 2005 because of an increase in leukocytes

(74 950 μL^{-1}). Using low dose hydroxyurea (dose ranging between 250 and 500 mg), leukocyte counts could easily be controlled during the following months. The patient was lost for follow-up in October 2005.

Discussion

Basophilia and eosinophilia are frequently detected in myeloproliferative neoplasms (MPN), especially in CML [1–10], whereas eosinophilia and basophilia are rarely found in patients with MDS. We describe a patient with MDS who developed a huge increase in eosinophils and metachromatic cells that were found to be basophils as determined by phenotyping and functional studies. Although an extensive panel of markers were applied, no molecular defect explaining eosinophil/basophil crisis could be detected. In a cohort of 322 patients with MDS, only one case presented with basophil/eosinophil transformation, suggesting that this type of progression is a rare event in MDS.

Of all 322 patients examined, several were found to develop moderate to extensive eosinophilia or moderate to extensive basophilia during disease progression. However, no further patient with mixed lineage (basophil and eosinophil) progression was identified in the group examined. The molecular mechanism leading to mixed lineage crisis in our patient remains unknown. In fact, although an extensive panel of molecular and cytogenetic markers were tested, no defect could be identified. A remarkable aspect was that the

increase in basophils and eosinophils was not accompanied by rapid deterioration or an increase in blasts. Rather, the clinical course in this patient was indolent. This argues against an unrelated reactive or allergic disease that would explain the development of basophilia and eosinophilia.

During the past few years, a number of useful novel basophil-related antigens have been developed and have been applied in clinical haematology [15,28,32–37]. Several markers are useful to confirm basophil lineage involvement in MDS and to exclude the presence of mast cells [15,28,33,34]. This is of particular interest as, in immature neoplasms, basophils can be confused with immature mast cells that may show bi- or poly lobed nuclei [11–15]. In the present study most, but not all, metachromatic cells could be classified as basophil granulocytes by morphology. As assessed by immunostaining, the basophil lineage was confirmed and the presence of neoplastic mast cells could be excluded. In fact, these cells were BB1+, 2D7+, KIT- cells. Clear expression of CD203c was also indicative of the basophil lineage, but is not a definitive sign of basophils, as mast cells can also express low amounts of CD203c [28,43].

In patients with mixed lineage MDS, MPN or MDS/MPN with an increase in metachromatic cells, especially in those with CMML, it is always important to exclude the presence of a coexistent systemic mastocytosis, SM (e.g. SM-MDS or SM-CMML), especially when patients present with eosinophilia. In such patients, mastocytosis may not necessarily be detected in bone marrow smears (no mast cells capable of aspiration) or peripheral blood studies. Therefore, in these patients, a thorough histologic and immunohistochemical examination of the bone marrow is required [32,44–46]. In our patient, histologic and molecular analyses were performed to exclude an underlying mast cell neoplasm. In fact, in these studies, no atypical mast cells, no compact mast cell infiltrates, and no *KIT* D816V mutation was detected.

Moreover, phenotyping excluded the presence of a pathological mast cell population in the bone marrow in our patient. These studies thus also excluded another important differential diagnosis, which is myelomastocytic leukaemia, a neoplasm defined by an increase in immature mast cells without evidence (criteria) for coexisting mastocytosis [12–14]. As immature mast cells, that often have bi- or multi-lobed nuclei, can be confused with basophils, it is important to take this differential diagnosis into account. In our 322 patients with MDS, 14 patients with a diagnostic increase in metachromatic cells ($\geq 10\%$) were identified. However, of these 14 patients, only two were found to fulfil the criteria of myelomastocytic leukaemia, whereas all other patients presented with an increase in basophils.

A useful screen marker for mast cells is tryptase. Basophils, by contrast, express only low amounts of the enzyme. It has also been described that tryptase is detectable in leukaemic basophils at low levels [33,34,37]. In our patient, a slightly elevated serum tryptase

was found, and metachromatic cells were also found to be slightly immunoreactive for tryptase. These data confirm the presence of basophils as mast cells display huge amounts of tryptase with highly elevated serum enzyme levels.

A number of specific cytogenetic and molecular defects are indicative of myeloid neoplasms presenting with eosinophilia, basophilia or an increase in both cell types (FIP1L1/PDGFR α , CBF β /NYH11, BCR/ABL, AML1/ETO) [26,47–50]. It has also been reported that eosinophils and/or basophils may increase in patients presenting with defects in the PDGFR [51]. However, although leukaemic cells were extensively studied, none of these defects were detected in our patient. Rather, this patient exhibited a normal karyotype and no known molecular defect at the time of progression.

A number of recent data suggest that eosinophilia and basophilia are of prognostic significance in MDS [52,53]. In one study, basophilia and eosinophilia were found to be associated with a significantly reduced probability of AML-free survival [52]. In another study, basophilia was found to correlate with low risk MDS, whereas transformation to AML was found to be associated with a lower number of basophils [53]. In our patient, mixed lineage crisis was not associated with other signs of rapid disease progression or an increase in blasts. Rather, the clinical course remained stable during the observation period. Nevertheless, because the clinical impact of chronic eosinophilia (organ damage, e.g. lung or cardiac fibrosis) was uncertain, we decided to apply mild cytoreduction using hydroxyurea. In response to low dose hydroxyurea, eosinophil and basophil counts decreased and could easily be kept under control without any side effects.

In summary, our data show that mixed lineage crisis involving basophils and eosinophils is a rare event in MDS. The molecular mechanisms underlying progression in our patient remain unknown.

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